

- 498 -

(3S)-3-[(3S)-2-Oxo-3-(3-phenylpropionylamino)-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609a).

5 **Step A.** A solution of 204 (223 mg, 0.5 mmol) and 603r (300mg; 0.36 mmol) in 4 ml of DMF and 4 ml of CH₂Cl₂ was treated with (Ph₃P)₂PdCl₂ (10 mg), 1-hydroxybenzotriazole (135 mg, 1.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
10 (115 mg, 0.6 mmol). Tri-n-butyl tin hydride (219 mg, 0.75 mmol) was added dropwise to the reaction and stirred for 18 h. The reaction was poured onto EtOAc and washed with aq. 10% NaHSO₄, sat. aq. NaHCO₃ and sat. aq. NaCl, dried over Na₂SO₄ and concentrated in
15 *vacuo*. Chromatography (flash, SiO₂, 0% to 50% EtOAc/hexane) gave 360 mg (86%) of 607a as a foam.

Step B. A solution of 607a (360 mg) in 5 ml of CH₂Cl₂ was added dropwise to a suspension of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodioxol-3(1H)-one (362 mg, 0.85
20 mmol) in 20 ml of CH₂Cl₂. The reaction was stirred for 4.5 h, diluted with CH₂Cl₂ and washed with a 1:1 mixture of sat. aq. NaHCO₃/sat. aq. Na₂S₂O₃, sat. aq. NaHCO₃ (2x) and sat. aq. NaCl, dried over Na₂SO₄ and concentrated in *vacuo*. Chromatography (flash, SiO₂,
25 20% EtOAc/CH₂Cl₂) gave 340 mg (95%) of the ketone 608a.

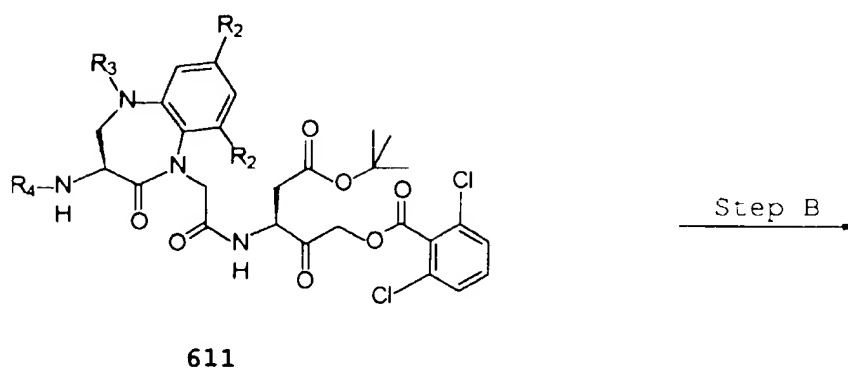
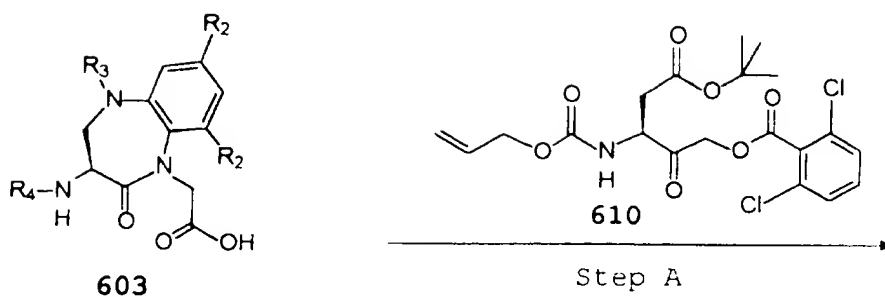
Step C. 608a (300 mg, 0.36 mmol) was dissolved in 25 ml of 25% TFA/CH₂Cl₂ and stirred at RT for 5 h and concentrated in *vacuo*. Chromatography (flash, SiO₂, 0 to 5% MeOH/CH₂Cl₂) gave 118 mg (42%) of 609a as a white
30 solid: ¹H NMR (CD₃OD) δ 7.62-6.65 (16H, m), 4.85-4.7

- 499 -

(1H, m), 4.68-4.42 (2H, m), 4.40-4.15 (2H, m), 3.48-3.28 (1H, m), 3.0-2.9 (1H, m), 2.9-2.6 (4H, m), 2.55-2.18 (3H, m), 2.16-1.96 (2H, m).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609b) was prepared from 603d in a similar manner as 609a to give 287 mg (43% overall yield) as white solid: ¹H NMR (DMSO-d₆) δ 1.6(s, 3H), 2.7-3.1(m, 2H), 3.45(m, 1H), 4.4(t, 1H), 4.7(m, 2H), 4.95(m, 1H), 5.2, 5.4(2s, 1H), 7.2-7.65(m, 8H), 7.9(d, 2H), 8.8(t, 1H), 8.9,9.1(2s, 1H), 12.6(br, 1H).

- 500 -



(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-methanesulfonyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (**612**) was prepared by a method similar as **607a**

5 (Steps A and C only) using **603m** (150 mg, 0.36 mmol)

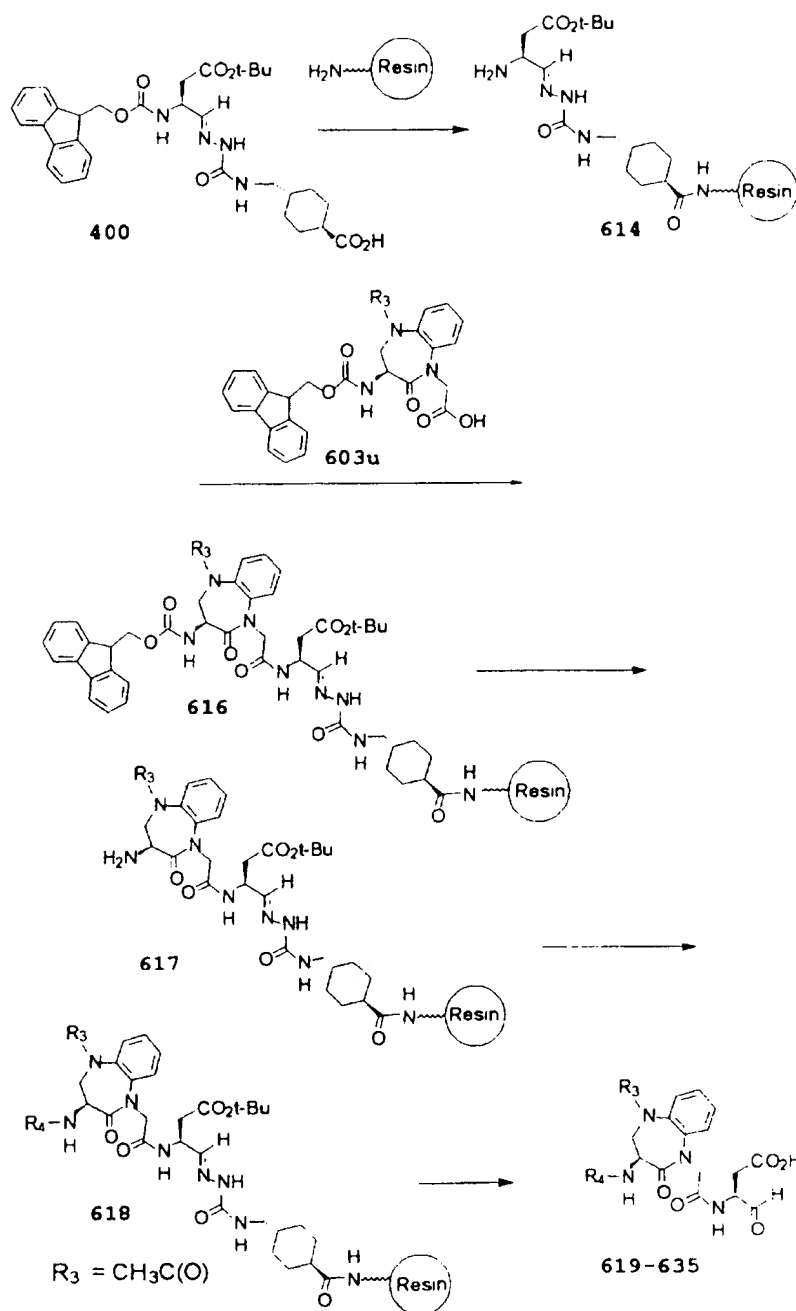
- 501 -

instead of **603r** and (3*S*)-3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoic acid *t*-butyl ester (110; 160 mg, 0.36 mmol, WO 93/16710) instead of **606a** to give **612** (56%) as a white solid: ¹H NMR
5 (CDCl₃) 7.85-7.10 (12H, m), 5.4-4.65 (4H, m), 4.6-4.15 (4H, m), 3.10-2.72 (5H, s & m).

Example 13

Compounds **619-635** were synthesized as described in Example 13 and Table 14.

- 502 -



- 503 -

Syntheses of 619-635.

Step A. Synthesis of 614. TentaGel S® NH₂ resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with dimethylformamide (3 X 50 mL),
5 10% (v/v) diisopropylethylamine (DIEA) in dimethylformamide (2 X 50 mL) and finally with dimethylformamide (4 X 50 mL). Sufficient dimethylformamide was added to the resin to obtain a slurry followed by 400 (1.42 g, 2.4 mmol, prepared from
10 (3S) 3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-hydroxybenzotriazole hydrate (HOBT·H₂O; 0.367 g, 2.4 mmol), O-benzotriazole-N,N,N,N'-tetramethyluronium
15 hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin was isolated on a sintered glass funnel by suction filtration and washed with dimethylformamide (3
20 X 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) acetic anhydride/dimethylformamide (2 X 25 mL) directly in the funnel (10 min/wash). The resin was washed with dimethylformamide (3 X 50 mL) and dichloromethane (3 X
25 50 mL) prior to drying overnight *in vacuo* to yield **614** (11.0 g, quantitative yield).

Step B. Synthesis of 616. Resin **614** (3.0 g, 0.16 mmol/g, 0.48 mmol) was swelled in a sintered glass funnel by washing with dimethylformamide (3 X 15 mL).
30 The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/dimethylformamide (15 mL) for 10 min

- 504 -

(intermittent stirring) and then for 20 min with fresh piperidine reagent (15 ml). The resin was then washed with dimethylformamide (3 X 15 ml), followed by N-methypyrrolidone (2 X 15 mL). After transferring the resin to a 100 mL flask, N-methypyrrolidone was added to obtain a slurry followed by **603u** (0.736 g, 0.72 mmol), HOBT·H₂O (0.112 g, 0.73 mmol), HBTU (0.27 g, 0.73 mmol) and DIEA (0.26 mL, 1.5 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin work-up and capping with 20% (v/v) acetic anhydride in dimethylformamide were performed as described for **614** to yield **616** (3.13 g, quantitative yield).

Step C. Synthesis of 617. This compound was prepared from resin **616** (0.24 g, 0.038 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **617**. The resin was washed with dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL).

Step D. Method 1. (624). Resin **617** was acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in N-methypyrrolidone (1 mL), a solution of 0.4M HBTU in N-methypyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with dimethylformamide (3 X 1 mL), dichloromethane (3 X 1 mL) and dried *in vacuo*.

- 505 -

The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H₂O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined
5 filtrates were added to cold 1:1 ether:pentane (12 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H₂O/0.1% TFA (15 mL) and lyophilized to obtain crude **624** as a white
10 powder. The compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5 μ , 21.4 X 250 mm) eluting with a linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were
15 pooled and lyophilized to provide **624** (10.0 mg, 54%).

Step D. Method 1A. Synthesis of 627. Following a similar procedure as method 1, resin **617** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described
20 in Step C and the free amine was acetylated with 20% (v/v) acetic anhydride in dimethylformamide (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2 hr at room temperature. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **627** (4.2
25 mg, 20%).

Step D. Method 2. Synthesis of 632. Following a similar procedure as method 1, resin **617** was acylated with 0.5M cinnamoyl chloride in N-methylpyrrolidone (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2
30 hr at room temperature. The acylation step was

- 506 -

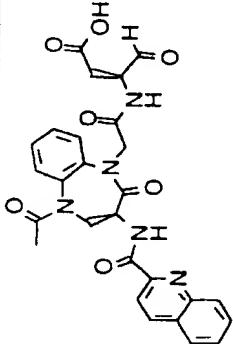
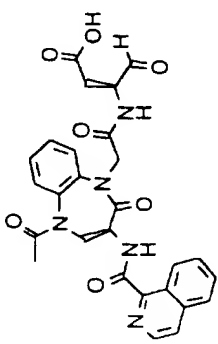
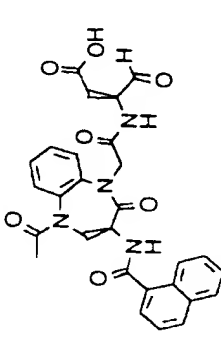
repeated. Cleavage of the aldehyde from the resin gave **632** (11.1 mg, 58%).

Step D. Method 3. Synthesis of 629. Following a similar procedure as method 1, resin **617** was reacted
5 with 1.0M benzenesulfonyl chloride in dichloromethane (0.5 mL) and 1M pyridine in dichloromethane (0.60 mL) for 4 hr at room temperature. The reaction was repeated. Cleavage of the aldehyde from the resin **629** (4.7 mg, 24%).

10 **Analytical HPLC methods:**

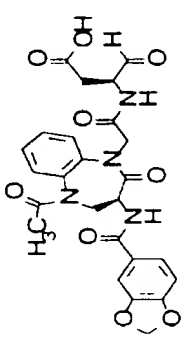
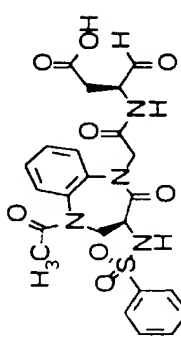
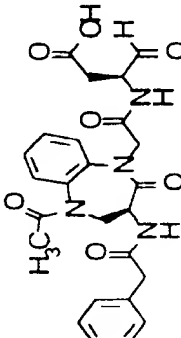
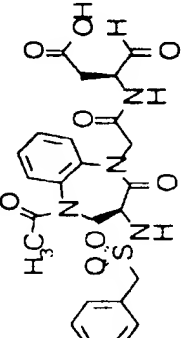
(1) Waters DeltaPak C18, 300A (5u, 3.9 X 150 mm).
Linear acetonitrile gradient (5% - 45%) containing 0.1%
TFA (v/v) over 14 min at 1 mL/min.

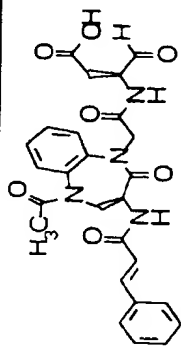
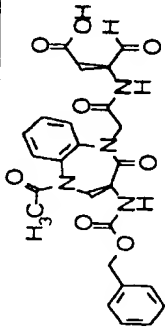
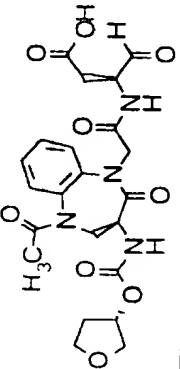
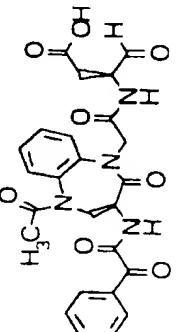
Table 14

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
619		C27H25N5O7	531.53	11.71 (1) 98%	532	1
620		C27H25N5O7	531.53	10.44 (1) 98%	532	1
621		C28H26N4O7	530.54	11.57 (1) 98%	(M+Na) + 553	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
622		C28H26N4O8	546.54	10.19 (1) 98%	(M+Na) + 569	1
623		C39H32N4O10	716.71	15.8 (1) 09%	(M-) 716	1
624		C22H22N4O7S	486.51	8.39 (1) 98%	487	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
625		C23H25N5O7S	515.55	7.60 (1) 98%	516	1
626		C25H26N4O8	510.51	7.58 (1) 98%	511	1
627		C26H27N5O8	537.53	7.96 (1) 98%	538	1A

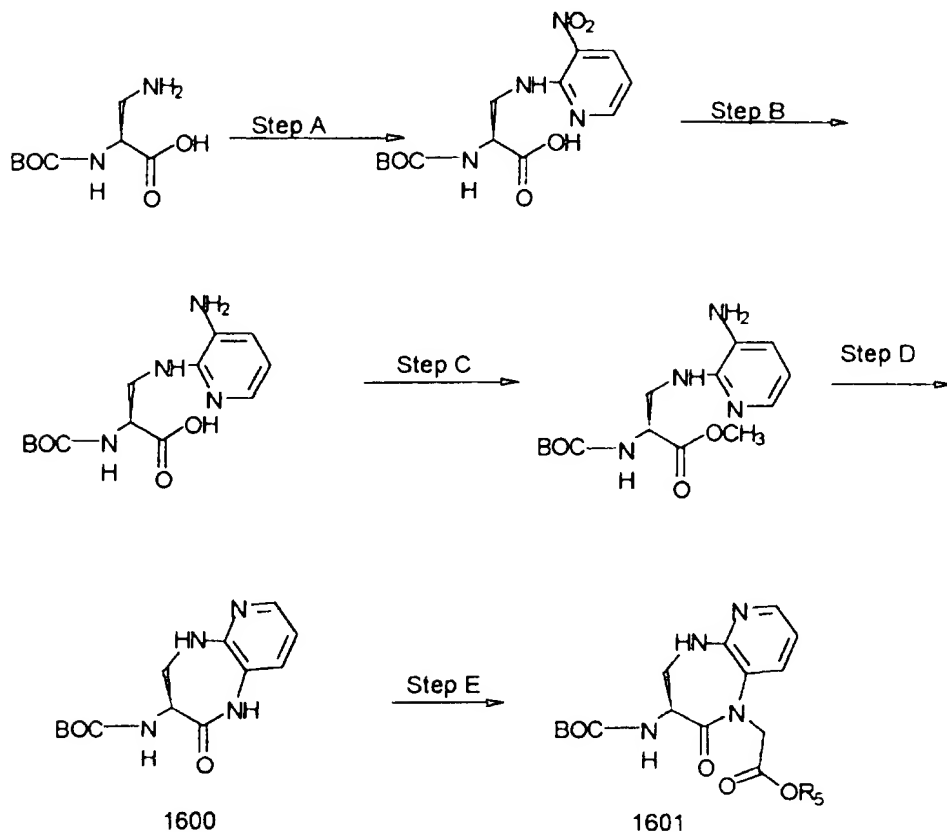
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
628		C ₂₅ H ₂₄ N ₄ O ₉	524.49	9.50 (1) 98%	525	1
629		C ₂₃ H ₂₄ N ₄ O ₈ S	516.53	9.85 (1) 98%	517	3
630		C ₂₅ H ₂₆ N ₄ O ₇	494.51	9.25 (1) 98%	495	2
631		C ₂₄ H ₂₆ N ₄ O ₈ S	530.56	10.19 (1) 98%	531	3

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
632		C26H26N4O7	506.52	10.99 (1) 98%	507	2
633		C25H26N4O8	510.51	11.48 (1) 98%	511	2
634		C22H26N4O9	490.47	6.87 (1) 98%	491	2
635		C25H24N4O8	508.49	10.03 (1) 98%	509	1

- 512 -

Example 14

Compounds 1605a-j, 1605m, 1605n, 1605p, 1605t, and 1605v were synthesized as described below.



(3S) N-(2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-pyrido [3,4-b][1,4-diazepine (1600)).

Step A. (2S) 2-tert-Butoxycarbonylamino-3-(3-nitropyridin-2-ylamino)propionic acid was prepared by a similar method as (2S) 2-tert-butoxycarbonylamino-3-(2-nitrophenyl-amino)propionic acid in Step A of the synthesis of 600a/103, except that 3-chloro-3-nitro pyridine was used instead of 2-

- 513 -

fluoronitrobenzene, to give 4.05 g (64%) of a yellow solid.

Step B. (2S) 2-tert-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid was prepared by a similar method to (2S) 2-tert-Butoxycarbonylamino-3-(2-aminophenylamino)-propionic acid in Step B of the synthesis of 600a/103 to give 3.68 g (quant.) as a dark solid.

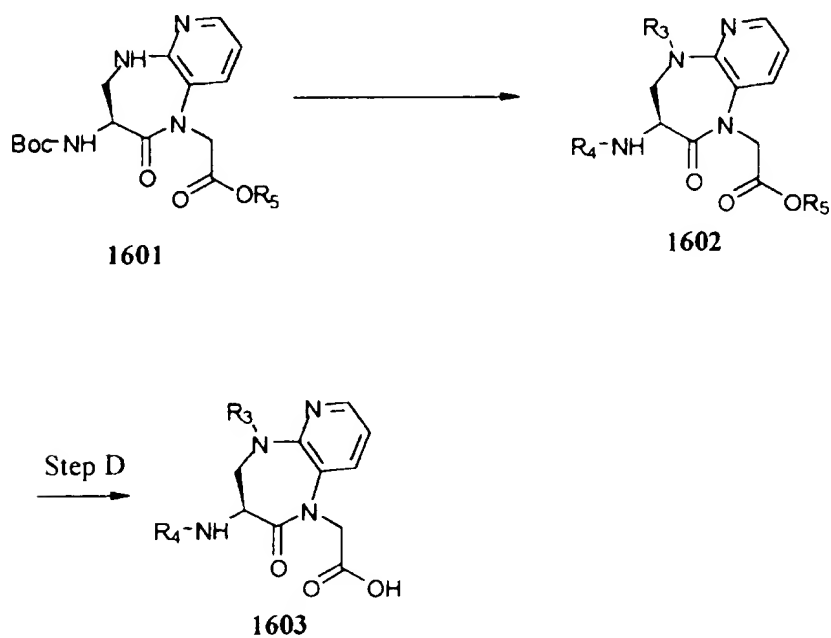
Step C. (2S) 2-tert-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester. A solution of (2S) 2-tert-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)-propionic acid (360 mg, 1.21 mmol) and MeOH (59 mg, 1.82 mmol) in anhydrous CH_2Cl_2 (20 ml) was treated with 4-dimethylaminopyridine (DMAP, 163 mg, 1.33 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (280 mg, 1.45 mmol). The reaction was stirred for 18 h, diluted with EtOAc (150ml), washed with water (2x), sat. aq. NaHCO_3 , and sat. aq. NaCl, dried over Na_2SO_4 and concentrated in vacuo. Chromatography (flash, SiO_2 , 0 to 5% MeOH/ CH_2Cl_2) gave 250 mg (67%) of the title compound as a light tan solid.

Step D. (3S) N-(2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-pyrido[3,4-b][1,4-diazepine (1600)). A solution of (2S) 2-tert-butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester (70 mg, 0.225 mol) and sodium methoxide/MeOH (130 μl , 0.56 mmol) in anhydrous MeOH (4 ml) was heated at 60°C for 16 h.

- 514 -

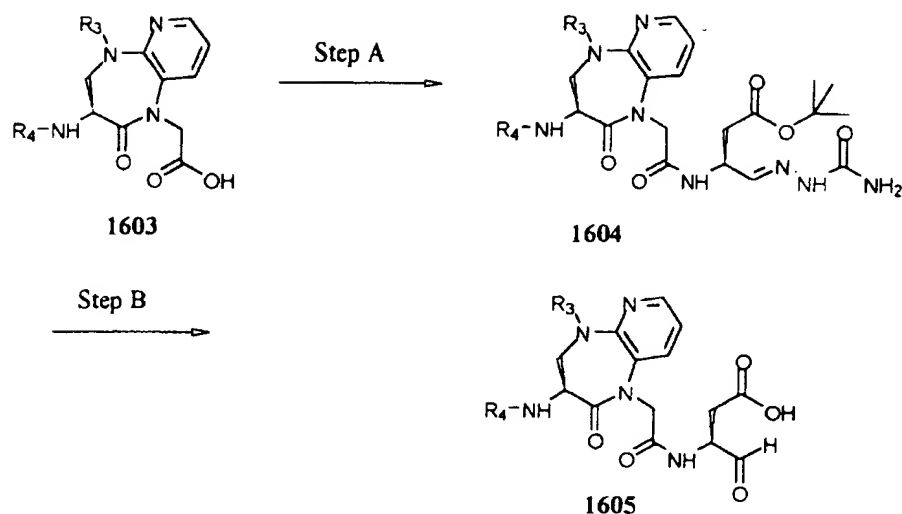
The reaction was concentrated *in vacuo*, the residue dissolved in 2 ml of H₂O and extracted with EtOAc (3x). The combined extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 0 to 3% MeOH/CH₂Cl₂) gave 7.5 mg (3%) of 1600 as a light tan solid: ¹H NMR (CD₃OD) δ 7.96-7.92 (1H, d), 7.75-7.65 (1H, br. s), 7.14-7.08 (1H, d), 6.73-6.65 (1H, m), 5.83-5.75 (1H, br. s), 5.4-5.25 (1H, br. s), 4.6-4.5 (1H, m), 3.95-3.84 (1H, m), 3.55-3.48 (1H, m), 1.4 (9H, s)

Step E. 1601 is prepared from 1600 following the method in Step D for the preparation 600a/103.



Synthesis of 1603. 1603 is prepared from 1601 following the methods for the synthesis of 603 from 600.

- 515 -



Synthesis of 1605. 1605 is prepared from 1603 by methods described for the synthesis of 605 from 603.

Table 15

1605	R ₃	R ₄
a	PhCH ₂ CH ₂ CO	PhCO
b	PhCH ₂ CO	PhCO
c	PhCO	PhCO
d	CH ₃ CO	PhCO
e	CH ₃ OCH ₂ CO	PhCO
f	(CH ₃) ₂ CHCH ₂ CO	PhCO
g	CH ₃ COCH ₂ CO	PhCO
h	CH ₃ OCOCO	PhCO
i	CH ₃ COCO	PhCO
j	CH ₃ OCO	PhCO
m	CH ₃ SO ₃	PhCO
n	CH ₃ CO	Naphthyl-2-CO
p	PhCH ₂ NHCO	PhCO

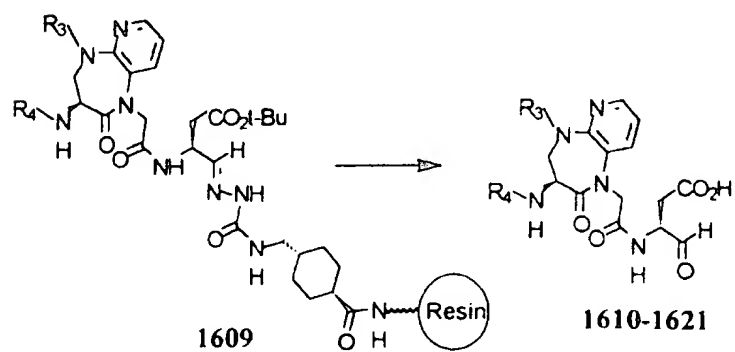
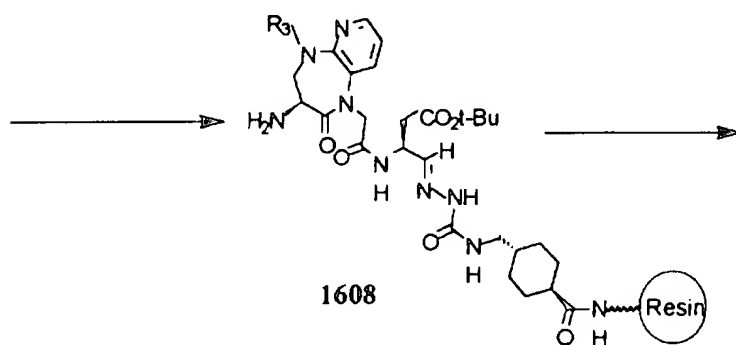
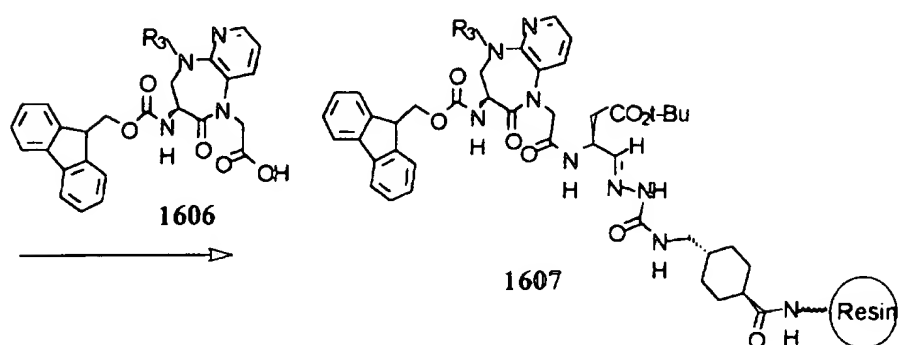
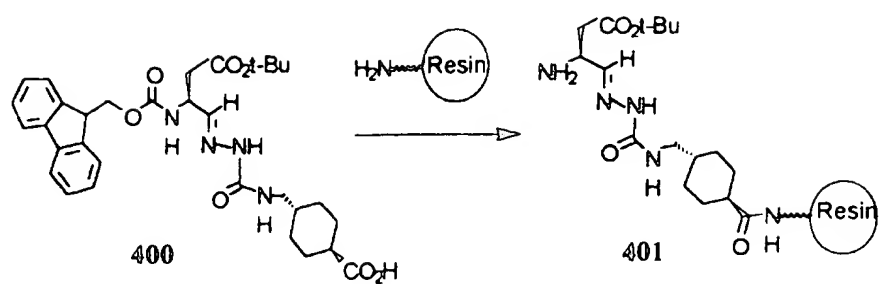
- 516 -

t	3-CH ₃ PhCH ₂ CO	PhCO
v	PhCH ₂ CH ₂ CO	PhCH ₂

Example 15

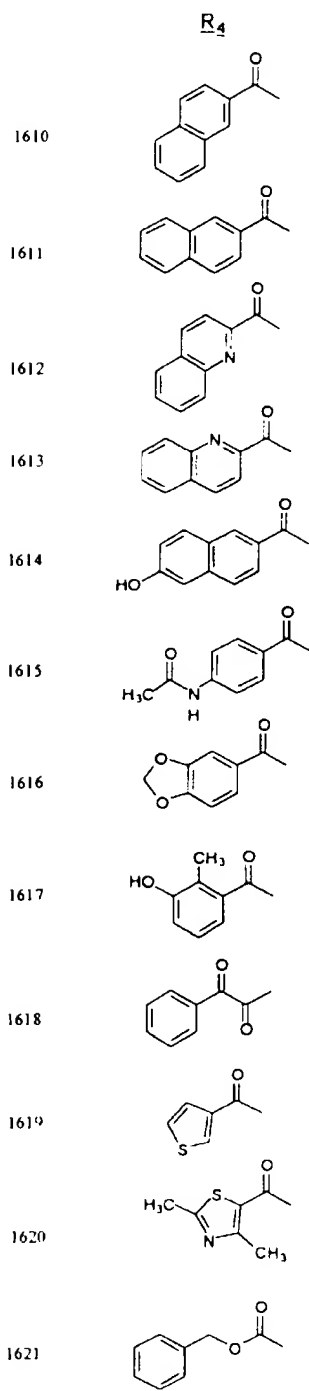
Compounds **1610-1621** are prepared from **1600**
5 by methods similar to the methods used to prepare
compounds **619-635** from **600a/103** and **600b**.

- 517 -



- 518 -

wherein for compounds 1610-1621,

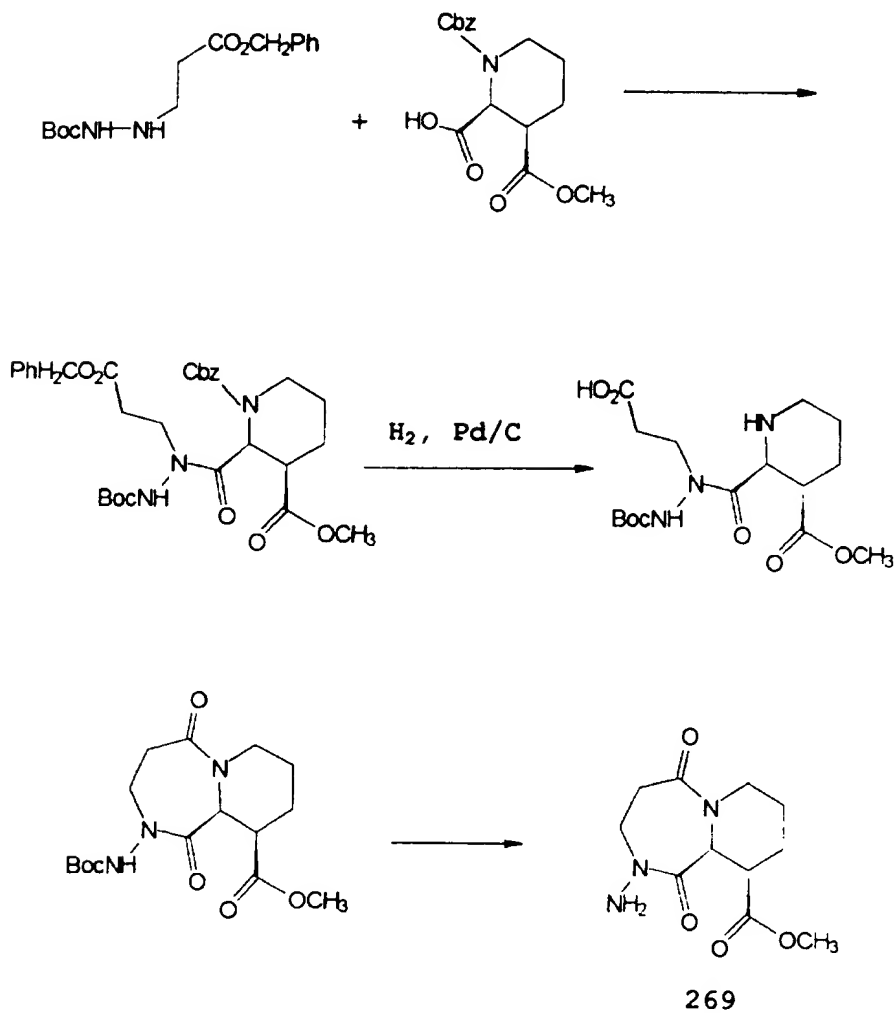
a $R_3 = \text{CH}_3\text{C}(\text{O})-$ b $R_3 = \text{CH}_3\text{OCH}_2\text{C}(\text{O})-$:

- 519 -

Example 16

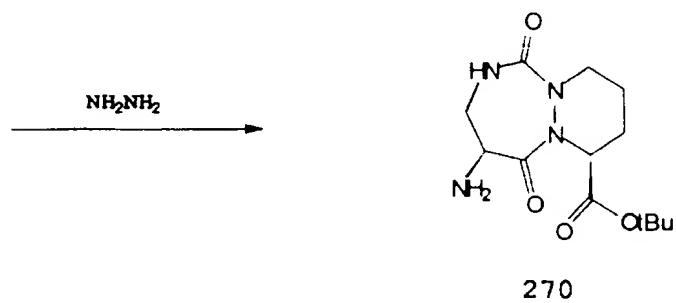
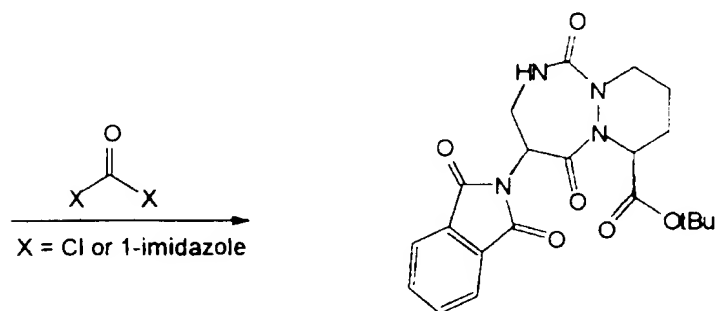
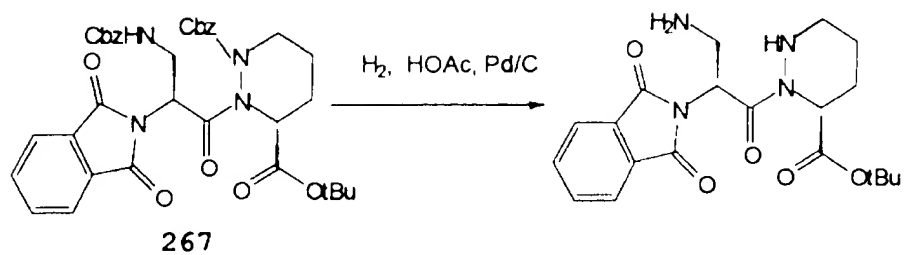
Compounds comprising scaffolds (e11), (y1), (y2), (z), and (e12) may be synthesized as described below.

- 5 **Synthesis of Scaffold R_1** , wherein R_1 is (e11) and wherein Y_2 is =O.



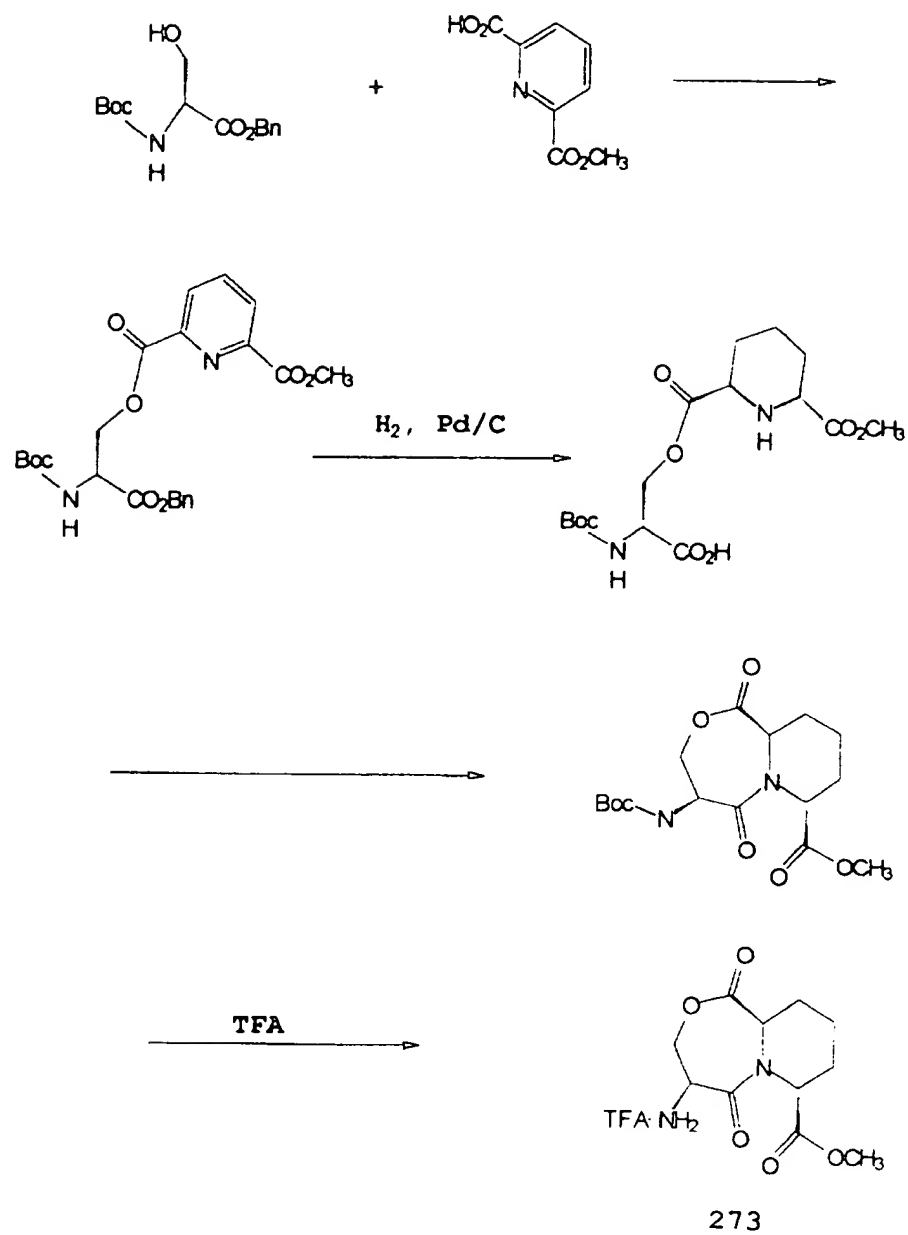
- 520 -

Synthesis of Scaffold R_1 , wherein R_1 is (y1) and wherein Y_2 is =O.

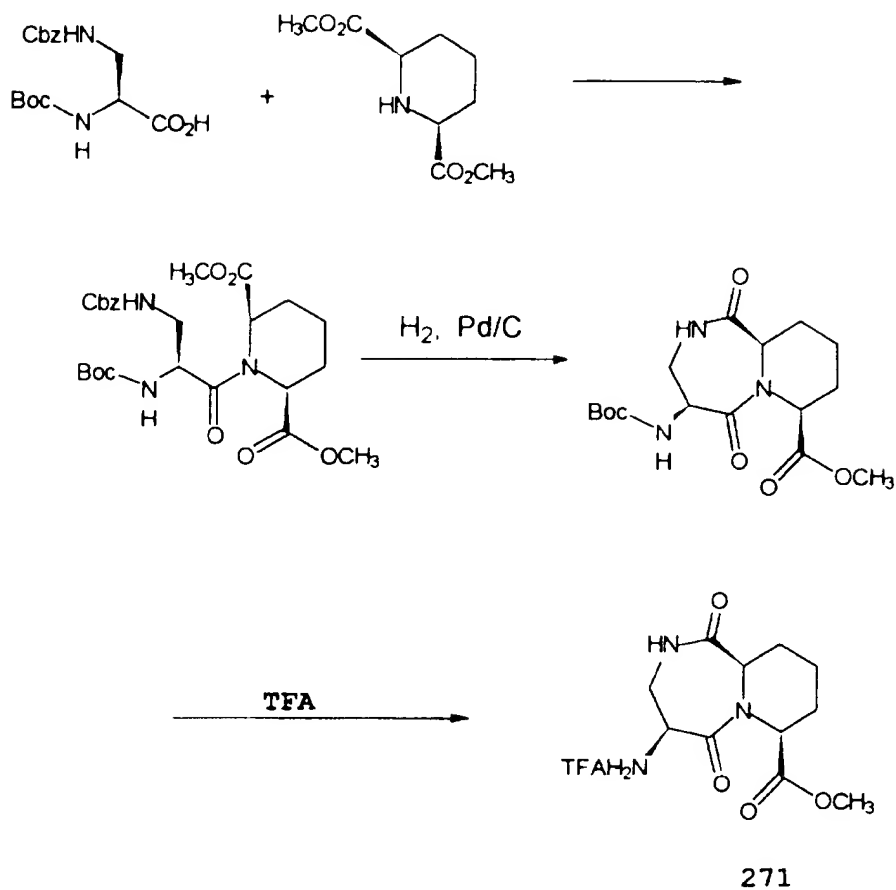


- 521 -

Synthesis of Scaffold R_1 , wherein R_1 is (y2) and wherein Y_2 is H_2 and X_7 is O.

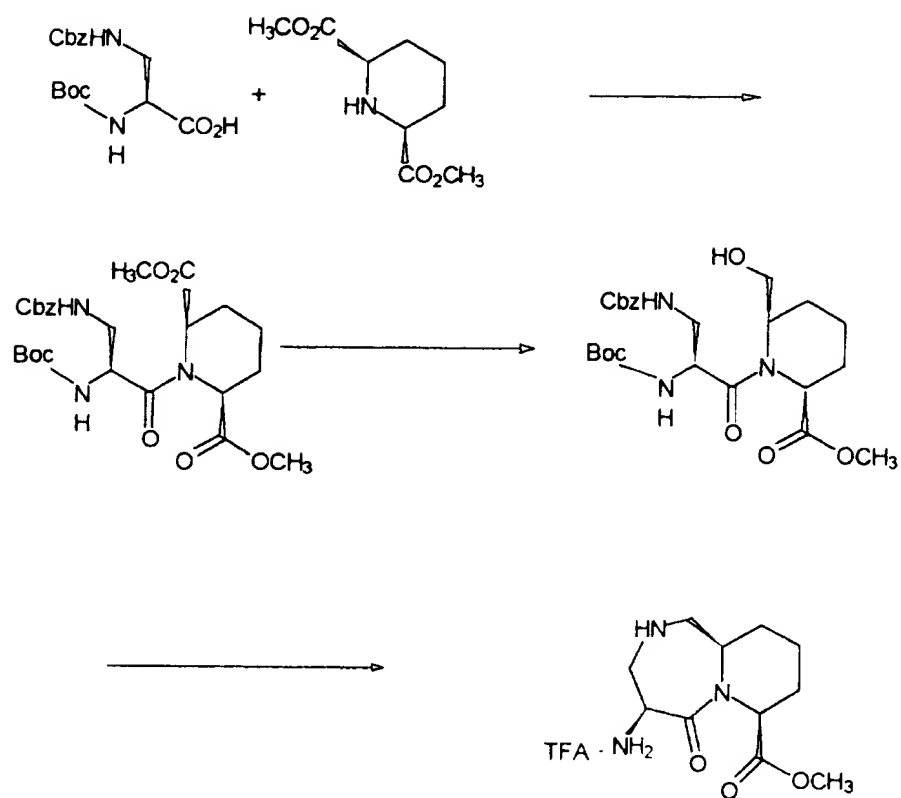


Synthesis of Scaffold R_1 , wherein R_1 is (y2) and wherein Y_2 is =O and X_7 is NH.



- 523 -

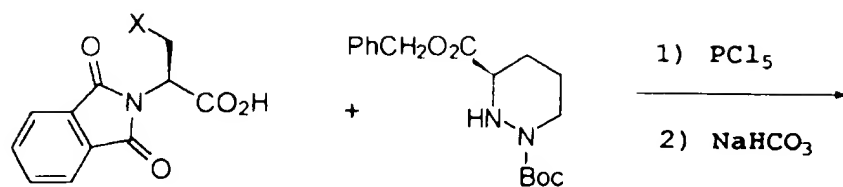
Synthesis of Scaffold R_1 , wherein R_1 is (y2) and wherein Y_2 is H_2 and X_7 is NH .



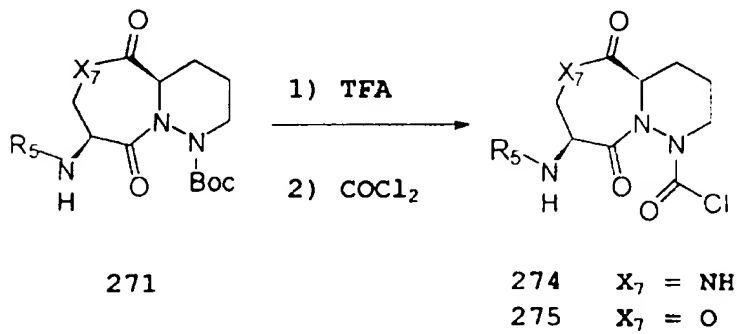
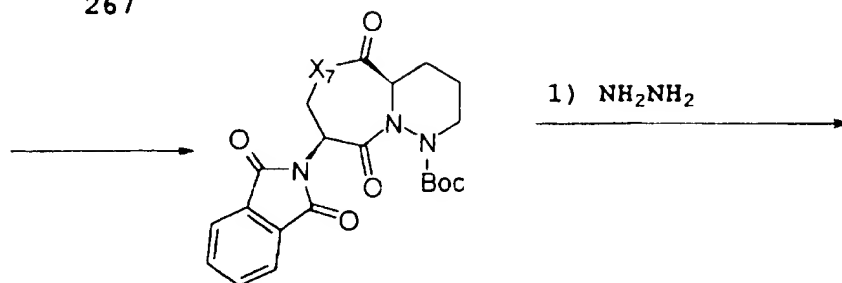
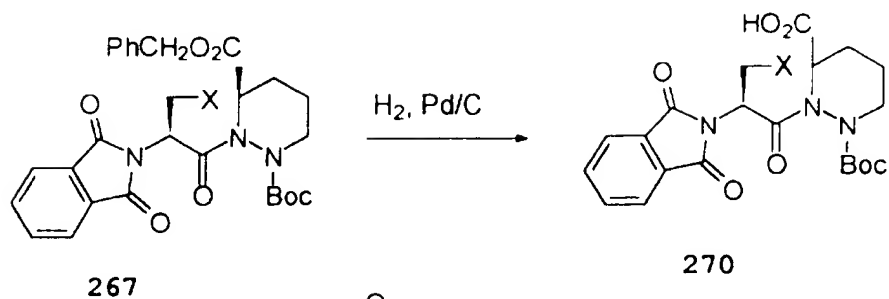
272

- 524 -

Synthesis of Scaffold R_1 , wherein R_1 is (z) and
wherein Y_2 is O.

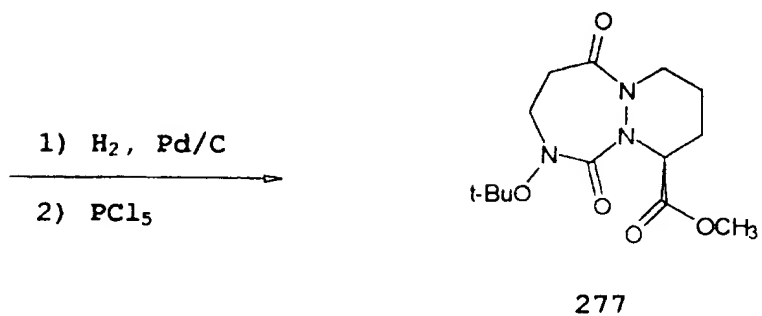
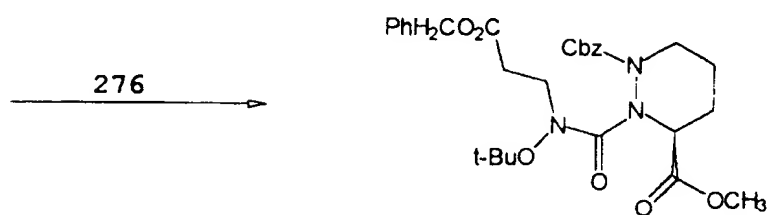
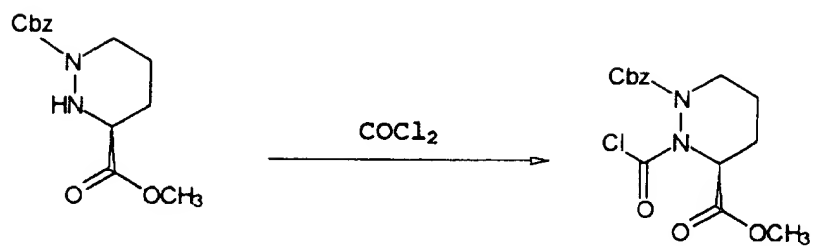
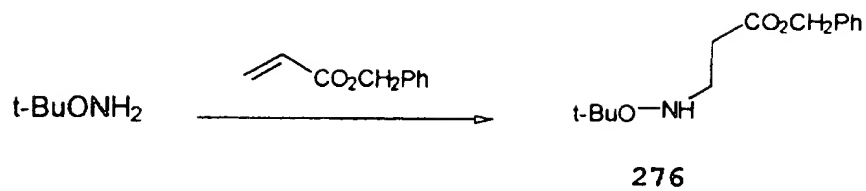


$X = \text{NHCBz}$
 $X = \text{OCH}_2\text{Ph}$



- 525 -

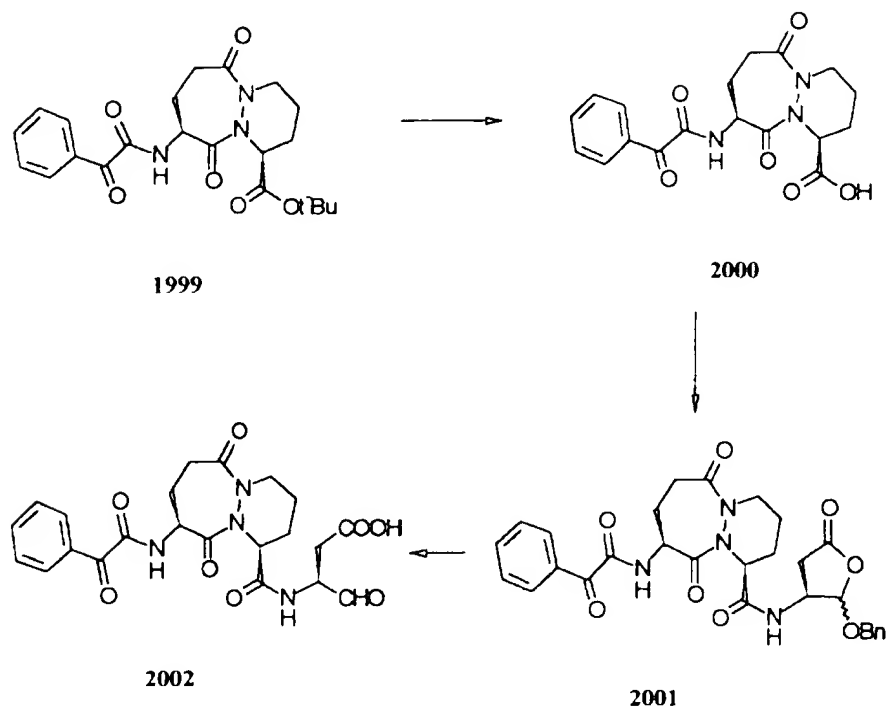
Synthesis of Scaffold R_1 , wherein R_1 is (e12) and wherein Y_2 is =O.



- 526 -

Example 17

The preparation of compounds 2001, 2002, 2100a-e, and 2201 is described below.



- (1S,9S) 9-Benzoylformylamino-6,10-dioxo-
- 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a]-[1,2]diazepine-1-carboxylic acid (2000). To a solution of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 340 mg, 1.15 mmol) in
- 10 CH₂Cl₂ was added benzoylformic acid (260 mg, 1.7 mmol), HOBt (230 mg, 1.7 mmol) and EDC (340 mg, 1.7 mmol). The resulting mixture was stirred at ambient temperature for 16 hours, poured into 1N HCl and extracted with CH₂Cl₂. The organic extracts were

- 527 -

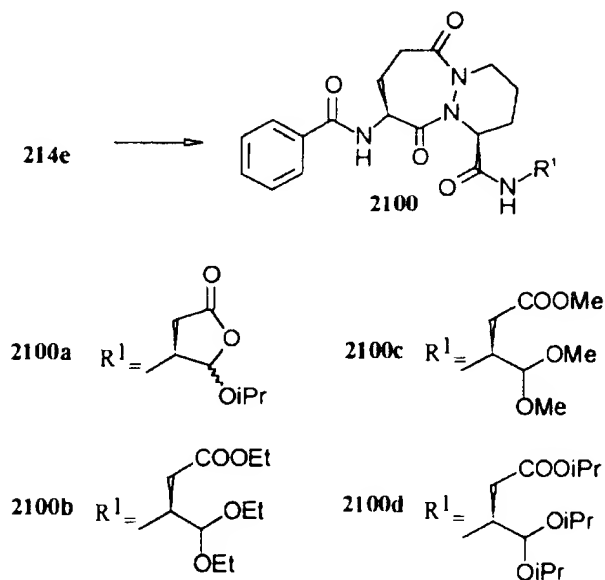
further washed with saturated NaHCO₃, dried over MgSO₄ and concentrated to afford **1999** as a pale yellow solid. The solid was dissolved in CH₂Cl₂ (25 ml) and TFA (25 ml) and stirred overnight and
5 concentrated in vacuo to give 560 mg of **2000** as an oil.

[**1S,9S(2RS,3S)**] 9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2(*R,S*)-benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]-
10 diazepine-1-carboxamide (**2001**), was synthesized from **2000** by methods similar to compound **213e** to afford 410 mg (63%) of **2001** as a white solid: ¹H NMR (CDCl₃; mixture of diastereomers) δ 8.25 (1H, d), 8.23 (1H, d), 7.78 (1H, dd), 7.65 (1H, bm), 7.50 (2H, m), 7.40-7.25 (4H, m), 6.55 (1H, d), 5.57 (1H, d),
15 5.10 (1H, t), 5.05-4.95 (2H, m), 4.90, (1H, d), 4.80 (1H, d), 4.72 (1H, bm), 4.65 (1H, m), 4.55 (1H, m), 4.45 (1H, t), 3.25 (1H, m), 3.15 (1H, m), 3.00 (2H, bm), 2.90 (1H, dd), 2.70 (1H, m), 2.47 (1H, dd), 2.45
20 (1H, m), 2.35 (1H, m), 2.00-1.75 (4H, m), 1.60 (1H, bm).

[**3S(1S,9S)**] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4-oxobutanoic acid (**2002**).
25 Compound **2001** (58.6 mg, 0.10 mmol) was treated with 15 ml of TFA/MeCN/water (1:2:3) and stirred at room temperature for 6.5 h. The reaction was extracted with ether. The aqueous layer was concentrated with azeotropic removal of the water using MeCN. The
30 product was suspended in CH₂Cl₂, concentrated in vacuo and precipitated with ether to give 46.8 mg

- 528 -

(99%) of **2002** as a white solid: ^1H NMR (CD_3OD) δ
 9.05 (0.25H, d), 8.15 (1H, d), 7.68 (1H, t), 7.64
 (0.25H, d), 7.55 (3H, t), 7.35 (0.5H, m), 5.22 (1H,
 t), 4.90 (1H, m), 4.58 (1H, dd), 4.50 (1H, m), 4.28
 5 (1H, bm), 3.45 (1H, m), 3.10 (1H, bt), 2.68 (1H,
 ddd), 2.60-2.45 (2H, m), 2.30 (1H, dd), 2.15-2.05
 (2H, m), 1.90 (2H, bm), 1.68 (1H, bm).



[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-N-(2-isopropoxy-5-oxo-
 10 tetrahydro-furan-3-yl)-6H-pyridazino-
 [1,2-a][1,2]diazepine-1-carboxamide (**2100a**). A
 solution of **214e** (101 mg, 0.23 mmol) in isopropanol
 (10 ml) was stirred at room temperature with a
 catalytic amount of *p*-toluenesulfonic acid (10 mg).
 15 After 75 minutes, the reaction mixture was poured
 into saturated NaHCO_3 and extracted with CH_2Cl_2 . The
 combined extracts were dried over Na_2SO_4 and

- 529 -

concentrated. Flash chromatography (SiO₂, CH₂Cl₂ to EtOAc) afforded 56 mg (51%) of **2100a** as a white solid: ¹H NMR (CDCl₃; mixture of diastereomers) δ 7.9-7.8 (2H,m), 7.6-7.5 (1H, m), 7.5-7.4 (2H, m), 7.1 (0.5H, d), 6.9 (0.5H, d), 6.4 (0.5H,d), 5.6 (0.5H, d), 5.3 (0.5H, s), 5.2-5.1 (1H, m), 4.95 (0.5H, m), 4.75-4.5 (1.5H, m), 4.35 (0.5H, t), 4.1 (0.5H, m), 3.98 (0.5H, m), 3.3-2.75 (4H, m), 2.5-2.4 (2H,m), 2.25 (1H, m), 2.1-1.9 (3H,m) 1.75-1.55 (2H,m).

- 10 **[3S(1S,9S)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diethoxy-butyrac acid, ethyl ester (2100b)**. A solution of **214e** (16 mg, 0.036 mmol) in ethanol (2 ml) was stirred at room
- 15 temperature with a catalytic amount of *p*-toluenesulfonic acid (2 mg). After 5 days, the reaction mixture was poured into saturated NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and concentrated. Flash
- 20 chromatography (SiO₂, CH₂Cl₂:EtOAc 95:5 v/v) afforded 16 mg (81%) of **2100b** as a white solid: ¹H NMR (CDCl₃) δ 7.85-7.74 (2H,m), 7.55-7.38 (3H,m), 7.04-6.95 (1H,d), 6.61-6.48 (1H,d), 5.15-5.08 (1H,m), 4.63-4.53 (1H,m), 4.52-4.45 (1H,m), 4.42-4.35 (1H,m),
- 25 4.15-4.05 (2H,m), 3.74-3.60 (2H,m), 3.57-3.42 (2H,m), 3.39-3.28 (1H,m), 3.03-2.93 (1H,m), 2.92-2.82 (1H,m), 2.65-2.52 (2H,m), 2.42-2.25 (1H,m), 2.20-1.88 (4H,m), 1.76-1.50 (2H,m), 1.35-1.10 (9H,m).

- [3S(1S,9S)] 3-(9-Benzoylformylamino-6,10-dioxo-**
- 30 **1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-dimethoxy-butyrac acid**

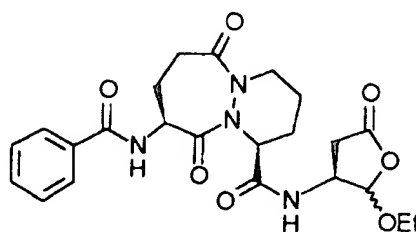
- 530 -

methyl ester (2100c). A solution of **214e** (165 mg, 0.37 mmol) in methanol (5 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (17.5 mg). After 4 days, the
5 reaction mixture was diluted with EtOAc and washed with 10% NaHCO₃ (3x) and brine. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography (SiO₂, EtOAc) afforded 127 mg (68%) of **2100c** as a white solid: ¹H NMR (CDCl₃) δ
10 7.82 (2H, d), 7.55-7.50 (1H, m), 7.47-7.43 (2H, m), 7.02 (1H, d), 6.53 (1H, d), 5.20-5.10 (1H, m), 4.56-4.50 (1H, m), 4.45-4.50 (1H each, two m), 3.69 (3H, s), 3.41 (3H, s), 3.43 (3H, s), 3.35-3.25 (1H, m), 3.06-2.98 (1H, m), 2.94-2.83 (1H, m), 2.65-2.53 (2H,
15 m), 2.35-2.32 (1H, m), 2.15-2.07 (1H, m), 2.00-1.89 (3H, m), 1.75-1.56 (2H, m).

**[3S(1S,9S)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diisopropoxy-butyric
20 acid, isopropyl ester (2100d).** A solution of **214e** (53 mg, 0.12 mmol) in isopropanol (5 ml) was stirred at 50 °C with a catalytic amount of *p*-toluenesulfonic acid (5 mg). After 3 days the reaction mixture was poured into saturated NaHCO₃ and extracted with
25 CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography (SiO₂, CH₂Cl₂:EtOAc (4:1 to 1:1 v/v)) afforded 49 mg (68%) of **2100d** as a white solid: ¹H NMR (CDCl₃) δ 7.85 (2H, d), 7.50-7.43 (1H, m), 7.41-7.35 (2H, m), 7.02 (1H, d), 6.47 (1H, d), 5.13-5.07 (1H, m) 5.00-4.9 (1H, m), 4.61-4.55 (2H, m), 4.37-4.30 (1H, m), 3.80-3.70 (1H, m), 3.90-3.80 (1H, m), 3.42-3.35 (1H, m),

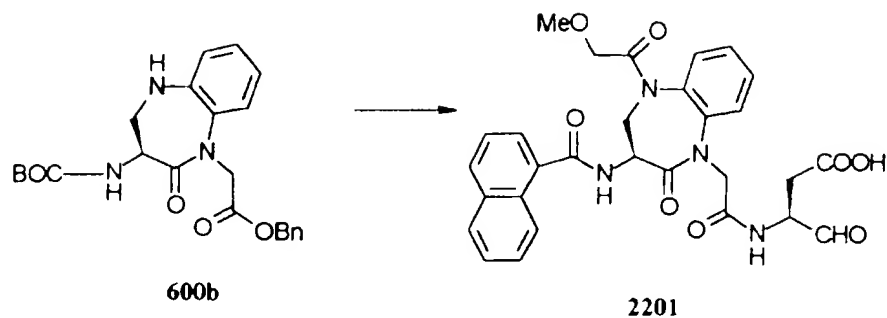
- 531 -

3.03-2.93 (1H, m), 2.91-2.81 (1H, m), 2.62-2.50 (2H, m), 2.38-2.33 (1H, m), 2.12-2.06 (1H, m), 1.97-1.81 (3H, m), 1.70-1.60 (2H, m), 1.28-1.05 (18H, m).

**2100e**

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-
 5 1,2,3,4,7,8,9,10-octahydro-*N*-(2-ethoxy-5-oxo-
 tetrahydro-furan-3-yl)-6*H*-pyridazino[1,2-*a*][1,2]-
 diazepine-1-carboxamide (2100e), was synthesized from
 302 via methods used to synthesize 304a to afford
 2100e, except ethanol and triethylorthoformate were
 10 used instead of methanol and trimethylorthoformate.
 Chromatography (SiO₂, 5% ethanol/CH₂Cl₂) afforded 92
 mg (68%) of a white solid: ¹H NMR (CDCl₃; mixture of
 diastereomers) δ 7.90-7.80 (2H, m), 7.60-7.50 (1H,
 m), 7.50-7.40 (2H, m), 7.30 (0.5H, d), 7.00 (0.5H,
 15 d), 6.50 (0.5H, d), 5.50 (0.5H, d), 5.20-5.10 (1.5H,
 m), 4.95 (0.5H, m), 4.75-4.65 (0.5H, m), 4.65-4.50
 (1H, m), 4.38 (0.05H, t), 4.00-3.90 (0.5H, m), 3.85-
 3.75 (0.5H, m), 3.75-3.65 (0.5H, m), 3.65-3.55 (0.5H,
 m), 3.30-2.70 (4H, m), 2.50-2.35 (2H, m), 2.30 (1H,
 20 d), 2.15-1.90 (3H, m), 1.80-1.60 (2H, m), 1.25-1.20
 (3H, two t)

- 532 -



(3*S*)-3-[(3*S*)-2-oxo-3-(1-naphthoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid

(2201) was synthesized from 600b by the methods used

5 to synthesize 605b to afford 2201: ^1H NMR (CDCl_3) δ
 8.30-8.22 (1*H*,m), 8.05-7.98 (1*H*, d), 7.96-7.83
 (1*H*,m), 7.77-7.68 (1*H*,m), 7.67-7.40 (7*H*,m), 5.12-5.02
 (1*H*,m), 4.98-4.41 (5*H*,m), 4.38-4.24 (1*H*,m), 4.07-4.00
 (1*H*,d), 3.92-3.80 (2*H*,m), 3.32 (3*H*,s), 2.75-2.60
 10 (1*H*,m), 2.58-2.35 (1*H*,m).

- 533 -

Example 18

We obtained the following data for selected compounds of this invention using the methods described herein (Table 16, see Example 7; Tables 17 and 18, see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

Table 16 Comparison of Prodrugs for Efficacy in LPS Challenged Mice: Inhibition of IL-1 β Production.

The percent inhibition of IL-1 β production after treatment with a compound of the invention is shown as a function of time after LPS challenge ("-" indicates that no value was obtained at that relative time).

		Time of Compound Administration (relative to time of LPS challenge, PO, 50 mg/kg)				
		Compound	-2h	-1h	0h	+1h
15		213f	(-4)	-	8	-
		213h	9	-	53	-
		213i	(-11)	-	62	-
20		213k	0	-	68	-
		213l	(-18)	-	80	-
		213m	26	-	42	-
25		213o	4	-	8	-
		213p	21	-	29	-
		213q	17	-	91	-
30		213r	59	-	37	-
		213x	0	-	78	-
		213y	29	-	50	-
35		214e	39	-	70	75
			43	44	48	11
			-	-	-	47
30		214k	12	-	31	-
		214l	0	-	54	-
		214m	0	-	17	-
35		214w	11	-	91	-
		264l	0	-	23	-
		404	-	-	-	56
		55	-	6	-	

- 534 -

	Compound	-2h	-1h	0h	+1h
5	412	0	-	0	-
		11	-	37	-
	418	-	-	-	64
		25	-	52	-
	434	-	-	-	80
10		0	-	63	-
	450	0	-	35	-
	452	-	-	-	70
		28	-	89	-
	456	-	-	-	56
15		41	-	69	-
	470	0	-	36	-
	471	0	-	34	-
	475	0	-	15	-
	481	27	-	0	-
20		19	-	15	-
	486	19	-	15	-
	487	17	-	20	-
	528	25	-	67	-
	550f	0	-	50	-
25		55	-	73	-
	550h	55	-	73	-
	550i	(-10)	-	23	-
	550k	36	-	34	-
	550l	9	-	38	-
30	550m	45	-	52	-
	550n	19	-	65	-
	550o	19	-	64	-
	550p	30	-	60	-
	655	0	-	68	-
35	656	31	-	16	-
	662	41	-	75	-
	668	-	-	-	53
	695a	49	-	78	-
	1015	15	-	28	-
35	2001	64	62	58	55
	2001a	10	-	16	-
	2002	5	-	87	-
	2100h	34	-	32	-
	2100i	19	-	74	-
35	2100j	48	41	0	33
	2100k	30	50	32	72
	2100l	52	-	28	-
	2100m	40	-	42	-
	2100n	21	9	64	73
	2100o	31	44	68	64

- 535 -

Table 17 Data for selected compounds of this invention obtained using the methods described in Examples 1-4.

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
213f			3000		
213g			2200		
213h			1500		
213i			1100		
213j					
213k			2000		
213l			2000		
213m			2500		
213o		5000	3300		
213p			<300		
213q			<300		
213r			<300		
213v	0.5	1,100	1100	41	23
213x		4500	2500		
213y			930		
214j	4.2	2500	6000		
214k	0.2	500	580		22
214l	6	1900	1100		12
214m	1.5	530	2200		33.4
214w	0.6	620	370		15
246b	30000	>30000		87	
264l			3000		
265a	2600	25000			
265c	1100	4500			32
265d	500	1500			35
265f	1200				24
280b		13000			
280c		10000			86
280d		25000			
283b		1750			41
283c		4000			50

- 536 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	283d		>8000	10000		
	308c	3000				
	308d	3000				
5	500	25	1800	1800		
	501	2.5	1800	1600		
	505c		1500			
	505d		>20000			
	505f		550			
10	510a	65	200		267	
	510d	2300	>20000			
	511c	730	>20000		78	40
	528			2200		
	550f			1100		
	550h			1800		
15	550i			1400		
	550k			3000		
	550l			750		
	550m			2000		
	550n			<300		
20	550o		450	3000		
	550p			2900		
	550q			700		
	640	155	2250	3900		
	642	35	8000	2900		
25	645	150				
	650	550	4000			
	653	30	2300	6000		
	655					
	656	0.6	2100	1600		2.9
30	662	0.5	1800	800		2.75
	668	9	5200	3700		29
	669	14		10000		
	670			4500		
	671	5	2000	2500		33.2
35	677			610		
	678	5	2700	2200		
	680					

- 537 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	681	9	3000	5000		
	682			1300		
	683	400	>20000	>20000		
	684	15	5000	2800		
5	686	4	4000	9000		
	688a			3000		
	688b			1300		
	689a	0.8	910	2500		
	689b	2.2	600	2000		
10	690a			1600		
	690b					
	691a	2.1	2900	1200		9.9
	691b	11.5	1,900	1400		
	692a					
15	692b			1800		
	693					
	694	3	2600	2100		
	695a					
	695b					
20	695c			2500		
	696	4.5	2000	2900		13
	700	275				
	701	90				
	702	45	>5000	20000		
25	703	5	1400	20000		
	704	30	2600	9800		
	705	5	2300	3200		
	706	5	2400	5800		
	707	180				
30	708	140				
	709	10	2100	14000		
	710	110				
	711	175				
	910	10	3400	3800		
35	911	9	3500	1900		
	912	10	4200	3800		
	913	4.5	2400	7000		

- 538 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	914	5.2	2600	2800		
	915	11.5	>8000	1900		
	918	7		1150		
	919	4	2000	4300		
5	920	16	2100	3000		
	921	8.5	1800	3000		
	1018	170	4000	5500		9.1
	1052	100	2500			16
	1053	27	2000	>20000		34
10	1056	170				17
	1075	120	5000	5500		14.5
	1095	360	6000			28
	1105	250	3500	3000		
	1106	75	4000	1700		
15	1107	65				
	1108	22	1400	2600		
	1109	80				
	1110	45				
	1111	18	6050	4400		
20	1112	3.5	1800	2300		
	1113	290				
	1114	125				
	1115	250				
	1116	215				
25	1117	35	1700	1300		
	1118	380				
	1119	515				
	1120	95				
	1121	170				
30	1122	400				
	1123	30	2,400	4500		
	1124	270				
	1125	55	2300	9000		
	2001a			3000		
35	2100f					
	2100g					
	2100h			2000		

- 539 -

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
2100i					
2100j	30000		12000		
2100k	520	4000	600		
2100l		750	2200		
2100m					
2100n	670	770	4000		
2100o	670	1150	1500		

We obtained the following data for selected compounds of this invention (Table 18) using the methods described herein (see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

Table 18

Cmpd.	Fluorescent Assay kinact m ⁻¹ s ⁻¹	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
286	370000	300	1600		119
505 b	190000	1500	2100	161	196
505 e	420000	9000	1000		

Example 19

In vivo acute assay for efficacy as
anti-inflammatory agent

Results in the Table 19 show that 412f, 412d and 696a inhibit IL-1 β production in LPS-challenged mice after oral administration using ethanol/PEG/water,

- 540 -

β -cyclodextrin, labrosol/water or cremophor/water as vehicles. The compound was dosed at time of LPS challenge. The protocol is described in Example 7.

5 Table 19 Inhibition (%) of IL-1 β production in LPS-challenged mice.

Compound	10 mg/kg dose	25 mg/kg dose	50 mg/kg dose
412f	17%	25%	32%
412e	5%	17%	61%
696a	0	45%	52%

10

Example 20Mouse Carrageenan Peritoneal Inflammation

Inflammation was induced in mice with an intraperitoneal (IP) injection of 10 mg carrageenan in 0.5 ml of saline (Griswold et al., Inflammation, 13, pp. 727-739 (1989)). Drugs are administered by oral gavage in ethanol/PEG/water, β -cyclodextrin, labrosol/water or cremophor/water vehicle. The mice are sacrificed at 4 hours post carrageenan administration, then injected IP with 2 ml of saline containing 50U/ml heparin. After gentle massage of the peritoneum, a small incision is made, the contents collected and volume recorded. Samples are kept on ice until centrifuged (130 x g, 8 mins at 4 °C) to remove cellular material, and the resultant supernatant stored at -20 °C. IL-1 β levels in the peritoneal fluid are determined by ELISA.

Results in the Table 20 show prodrug 412f inhibits IL-1 β production in carrageenan-challenged mice after oral administration of drug. Compound 214e

- 541 -

did not inhibit IL-1 β production when dosed orally at 50 mg/kg.

Table 20 Inhibition (%) of IL-1 β production by **412f** and **412d** in carrageenan-challenged mice.

5	Dose (mg/kg)	Compound 412f	Compound 412d
	1	30%	0
	10	54%	32%
	25	49%	31%
10	50	73%	36%
	100	75%	53%

Example 21

Type II Collagen-induced Arthritis

- 15 Type II collagen-induced arthritis was established in male DBA/1J mice at described Wooley and Geiger (Wooley, P.H., Methods in Enzymology, 162, pp. 361-373 (1988) and Geiger, T., Clinical and Experimental Rheumatology, 11, pp. 515-522 (1993)).
- 20 Chick sternum Type II collagen (4 mg/kg in 10 mM acetic acid) was emulsified with an equal volume of Freund's complete adjuvant (FCA) by repeated passages (400) between two 10 ml glass syringes with a gauge 16 double-hub needle. Mice were immunized by intradermal
- 25 injection (50 μ l; 100 μ l CII per mouse) of collagen emulsion 21 days later at the contra-lateral side of the tail base. Drugs were administered twice a day (10, 25 and 50 mg/kg) by oral gavage approximately 7 h apart. Vehicles used included ethanol/PEG/water, β -
- 30 cyclodextrin, labrosol/water or cremophor/water. Drug treatments were initiated within 2 h of the CII booster

- 542 -

immunization. Inflammation was scored on a 1 to 4 scale of increasing severity on the two front paws and the scores are added to give the final score.

Results in the Figs. 12, 13 and 14 show
5 prodrugs 412f, 412d and 696a inhibit inflammation in collagen-induced arthritits in mice after oral adminstration. Compound 214e did not inhibit inflammation when dosed (50 mg/kg) once a day by oral gavage.

10

Example 22

In vivo bioavailability determination

The drugs (10-100 mg/kg) were dosed orally to rats (10 mL/kg) in ethanol/PEG/water, β -cyclodextrin, labrosol/water or cremophor/water. Blood samples were
15 drawn from the carotid artery at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing, centrifuged to plasma and stored at -70°C until analysis. Aldehyde concentrations were determined using an enzymatic assay. Pharmacokinetic analysis of data was performed
20 by non-linear regression using RStrip (MicroMath Software, UT). Drug availability values were determined as follows: (AUC of drug after oral prodrug dosing/AUC of drug after i.v. dosing of drug)x(dose i.v./dose p.o.) x100%.

25

Results in Table 21 show that prodrugs 412f, 412d and 696a give significant blood levels of drug and have good drug availability when dosed orally. Blood levels of 214e were not detected when it was dosed orally.

- 543 -

Table 21 Oral Bioavailability of 412f, 412d, 696a and 214e in Rat.

Compound	Dose (mg/kg)	Cmax (μ g/ml)	Drug Availability (%)
412f	25	2.4	32
412d	25	2.6	35
696a	50	1.2	10
214e	45	0.2	0.9%

Example 23

ICE cleaves and activates pro-IGIF

10 ICE and ICE homolog expression plasmids

A 0.6 kb cDNA encoding full length murine pro-IGIF (H. Okamura et al., *Nature*, 378, p. 88 (1995)) was ligated into the mammalian expression vector pCDLSR α (Y. Takebe et al., *Mol. Cell Biol.*, 8, p. 466

15 (1988)).

Generally, plasmids (3 μ g) encoding active ICE (above), or the three ICE-related enzymes TX, CPP32, and CMH-1 in the pCDLSR α expression vector (C. Faucheu et al., *EMBO*, 14, p. 1914 (1995); Y. Gu et al., *EMBO*, 14, p. 1923 (1995); J. A. Lippke et al., *J. Biol. Chem.*, 271, p. 1825 (1996)), were transfected into subconfluent monolayers of Cos cells in 35-mm dishes using the DEAE-dextran method (Y. Gu et al., *EMBO J.*, 14, p. 1923 (1995)). Twenty-four hours later, cells were lysed and the lysates subjected to SDS-PAGE and immunoblotting using an antiserum specific for IGIF (H. Okamura et al., *Nature*, 378, p. 88 (1995)).

Polymerase chain reaction was used to introduce Nde I sites at the 5' and 3' ends of the murine pro-IGIF cDNA using the following primers: GGAATTCCATATGGCTGCCATGTCAGAAGAC (forward) and GGTAAACCATATGCTAACTTTGATGTAAGTTAGTGAG (reverse). The

- 544 -

resulting NdeI fragment was ligated into E. coli expression vector pET-15B(Novagen) at the NdeI site to create a plasmid that directs the synthesis of a polypeptide of 213 amino acids consisting of a 21-residue peptide (MGSSHHHHHHSSGLVPRGSHM, where LVPRGS represents a thrombin cleavage site) fused in-frame to the N-terminus of pro-IGIF at Ala2, as confirmed by DNA sequencing of the plasmid and by N-terminal sequencing of the expressed proteins. E. coli strain BL21(DE3) carrying the plasmid was induced with 0.8 mM isopropyl-1-thio- β -D-galactopyranoside for 1.5 hours at 37°C, harvested, and lysed by microfluidization (Microfluidic, Watertown, MA) in Buffer A (20 mM sodium phosphate, pH 7.0, 300 mM NaCl, 2 mM dithiothreitol, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride, and 2.5 μ g/ml leupeptin). Lysates were cleared by centrifugation at 100,000 x g for 30 min. (His)6-tagged pro-IGIF protein was then purified from the supernatant by Ni-NTA-agarose (Qiagen) chromatography under conditions recommended by the manufacturer.

In Vitro pro-IGIF Cleavage Reactions

In vitro cleavage reactions (30 μ l) contained 2 μ g of purified pro-IGIF and various concentrations of the purified proteases in a buffer containing 20 mM Hepes, pH 7.2, 0.1% Triton X-100, 2 mM DTT, 1 mM PMSF and 2.5 μ g/ml leupeptin and were incubated for 1 hour at 37°C. Conditions for cleavage by granzyme B were as described previously (Y. Gu et al., J. Biol. Chem., 271, p. 10816 (1996)). Cleavage products were analyzed by SDS-PAGE on 16% gels and Coomassie Blue staining, and were subjected to N-terminal amino acid sequencing

- 545 -

using an ABI automated peptide sequencer under conditions recommended by the manufacturer.

Kinetic Parameters of IGIF Cleavage by ICE

The kinetic parameters (k_{cat}/K_M , K_M , and k_{cat}) for IGIF cleavage by ICE were determined as follows. ³⁵S-methionine-labeled pro-IGIF (3000 cpm, prepared by *in vitro* transcription and translation using, the TNT T7-coupled reticulocyte lysate system (Promega) and pro-IGIF cDNA in a pSP73 vector as template) were incubated in reaction mixtures of 60 μ l containing 0.1 to 1 nM recombinant ICE and 190 nM to 12 μ M of unlabeled pro-IGIF for 8-10 min at 37°C. Cleavage product concentrations were determined by SDS-PAGE and PhosphoImager analyses. The kinetic parameters were calculated by nonlinear regression fitting of the rate vs. concentration data to the Michaelis-Menten equation using the program Enzfitter (Biosoft).

IFN- γ Induction Assays

A.E7 Th1 cells (H. Quill and R. H. Schwartz, *J. Immunol.*, 138, p. 3704 (1987)) (1.3×10^5 cells in 0.15 ml Click's medium supplemented with 10% FBS, 50 μ M 2-mercaptoethanol and 50 units/ml IL-2) in 96-well plates were treated with IGIF for 18-20 hours and the culture supernatant were assayed for IFN- γ by ELISA (Endogen, Cambridge, MA).

Example 24

Processing of pro-IGIF by ICE in Cos Cells

Cos cells were transfected with various expression plasmid combinations as described in Example 23. Transfected Cos cells (3.5×10^5 cells in a 35-mm dish) were labeled for 7 hours with 1 ml of methionine-

- 546 -

free DMEM containing 2.5% normal DMEM, 1% dialyzed fetal bovine serum and 300 $\mu\text{Ci/ml}$ ^{35}S -methionine (^{35}S -Express Protein Labeling-Mix, New England Nuclear). Cell lysates (prepared in 20 mM Hepes, pH 7.2, 150 mM NaCl, 0.1% Triton X-100, 5 mM N-ethylmaleimide, 1 mM PMSF, 2.5 $\mu\text{g/ml}$ leupeptine) or conditioned medium were immunoprecipitated with an antiIGIF antibody that recognizes both the precursor and the mature forms of IGIF (H. Okamura et al., Nature, 378, p. 88 (1995)). Immunoprecipitated proteins were analyzed by SDS-PAGE (polyacrylamide gel electrophoresis) and fluorography (Fig. 2A).

We also measured the presence of IFN- γ inducing activity in the cell lysates and the conditioned media of transfected cells (Fig. 2B). Transfected Cos cells (3.5×10^5 cells in a 35-mm dish) were grown in 1 ml medium for 18 hours. Media was harvested and used at 1:10 final dilution in the IFN- γ induction assay (Example 23). Cos cell pellets from the same transfection were lysed in 100 μl of 20 mM Hepes, pH 7.0, by freeze-thawing 3 times. Lysates were cleared by centrifugation as described above and were used at a 1:10 dilution in the assay.

Example 25

IGIF is a physiological substrate of ICE

Wild type (ICE+/+) and ICE-/- mice were primed with heat-inactivated *P. acnes*, and Kupffer cells were isolated from these mice 7 days after priming and were then challenged with 1 $\mu\text{g/ml}$ LPS for 3 hours. The amounts of IGIF in the conditioned media were measured by ELISA.

- 547 -

Wild type or ICE-deficient mice were injected intraperitoneally with heat-killed p. acnes as described (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995)). Kupffer cells were prepared seven
5 days later according to Tsutsui et al. (H. Tsutsui et al., Hepato-Gastroenterol., 39, p. 553 (1992)) except a nycodenz gradient was used instead of metrizamide. For each experiment, Kupffer cells from 2-3 animals were pooled and cultured in RPMI 1640 supplemented with 10%
10 fetal calf serum and 1 µg/ml LPS. Cell lysates and conditioned medium were prepared 3 hours later.

Kupffer cells from wild type and ICE-/- mice were metabolically labeled with ³⁵S-methionine as for Cos cells (described above in Example 24) except that
15 methionine-free RPMI 1640 was used in place of DMEM. IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media and immunoprecipitates were analyzed by SDS-PAGE and fluorography as described in Example 23. See Fig. 3.

20

Example 26Induction of IFN-γ Production In Vivo

LPS mixed with 0.5% carboxymethyl cellulose in PBS, pH 7.4, was administered to mice by intraperitoneal injection (30 mg/kg LPS) in a dose
25 volume of 10 ml/kg. Blood was collected every 3 h for 24 h from groups of three ICE-deficient or wild type mice. Serum IFN-γ levels were determined by ELISA (Endogen).

- 548 -

Example 27IGIF and IFN- γ Inhibition Assays

Inhibition of IGIF processing by ICE inhibitors was measured in ICE inhibition assays as described herein (see Example 1 and Table 22).

Human PBMC Assays

Human buffy coat cells were obtained from blood donors and peripheral blood mononuclear cells (PBMC) were isolated by centrifugation in LeukoPrep tubes (Becton-Dickinson, Lincoln Park, NJ). PBMC were added (3×10^6 /well) to 24 well Corning tissue culture plates and after 1 hr incubation at 37°C, non-adherent cells were removed by gently washing. Adherent mononuclear cells were stimulated with LPS (1 μ g/ml) with or without ICE inhibitor in 2 ml RPMI-1640-10% FBS. After 16-18 hr incubation at 37°C, IGIF and IFN- γ were quantitated in culture supernatants by ELISA.

For example, we obtained the following data for compound 412 of this invention using the methods described herein. The structure of compound 412 is shown below.

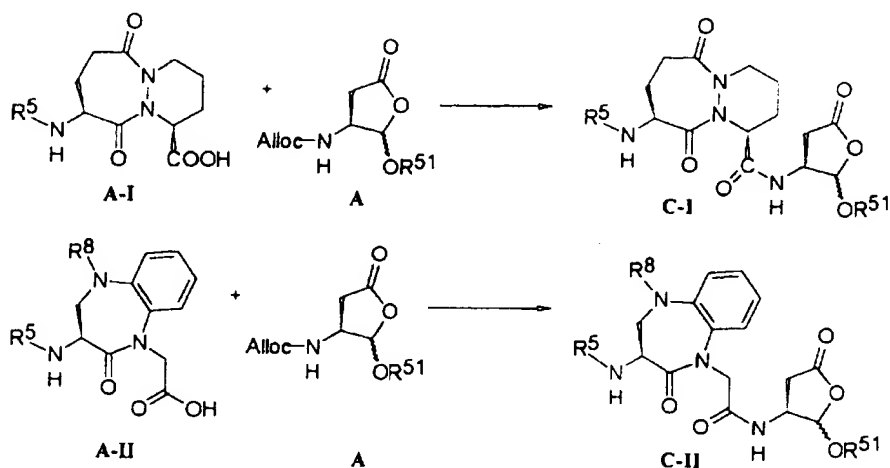
Table 22

compound	UV-Visible K_i (nM)	Cell PBMC avg. IC50 (nM)
412	1.3	580

- 549 -

Example 28

Compounds of this invention may be prepared via various methods. The following illustrates a preferred method:



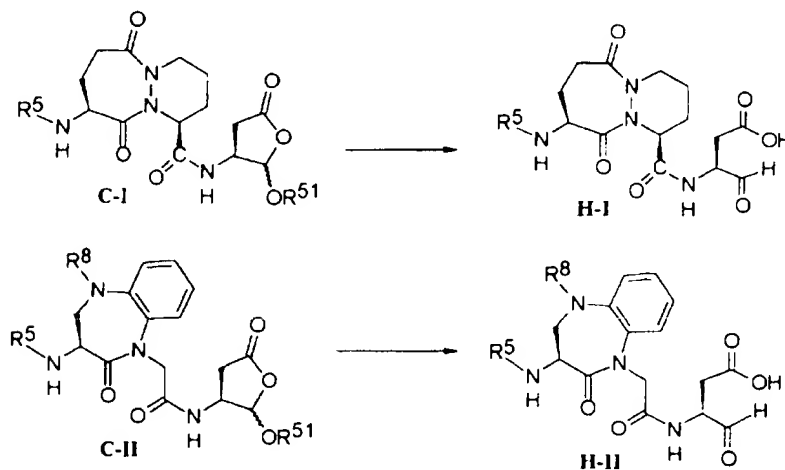
5 To a solution of **A** (1.1 equivalent) in CH₂Cl₂ (or DMF, or CH₂Cl₂:DMF (1:1)) is added triphenylphosphine (0-0.5 equivalent), a nucleophilic scavenger (2-50 equivalents) and tetrakis-
 10 triphenylphosphine palladium(0) (0.05-0.1 equivalent) at ambient temperature under inert atmosphere (nitrogen or argon). After 10 minutes, the above reaction mixture is optionally concentrated, then a solution of acid **A-I** or **A-II** in CH₂Cl₂ (or DMF, or CH₂Cl₂:DMF (1:1)) is added followed by addition of HOBT (1.1 equivalent)
 15 and EDC (1.1 equivalent). The resulting reaction mixture is allowed to stir at ambient temperature 1 hour-48 hours to provide coupled products **C-I** or **C-II**.

Various nucleophilic scavengers may be used in the above process. Merzouk and Guibe, Tetrahedron Letters, 33, pp. 477-480 (1992); Guibe and Balavoine, Journal of Organic Chemistry, 52, pp. 4984-4993
 20

- 550 -

(1987)). Preferred nucleophilic scavengers that may be used include: dimedone, morpholine, trimethylsilyl dimethylamine and dimethyl barbituric acid. More preferred nucleophilic scavengers are trimethylsilyl dimethylamine (2-5 equivalents) and dimethyl barbituric acid (5-50 equivalents). When the nucleophilic scavenger is trimethylsilyl dimethylamine, the above reaction mixture must be concentrated prior to addition of **A-I** or **A-II**.

10 Other compounds of this invention may be prepared by hydrolyzing compounds represented by **C-I** and **C-II** to compounds represented by **H-I** and **H-II** as described in the following scheme:



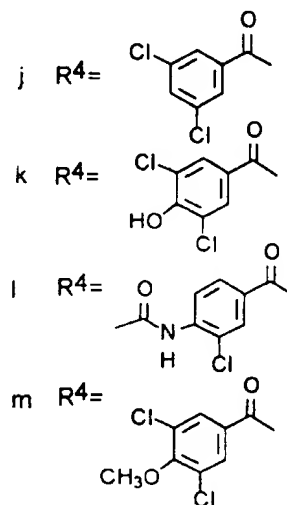
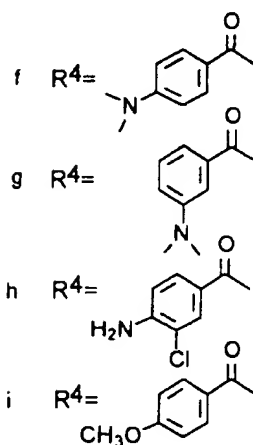
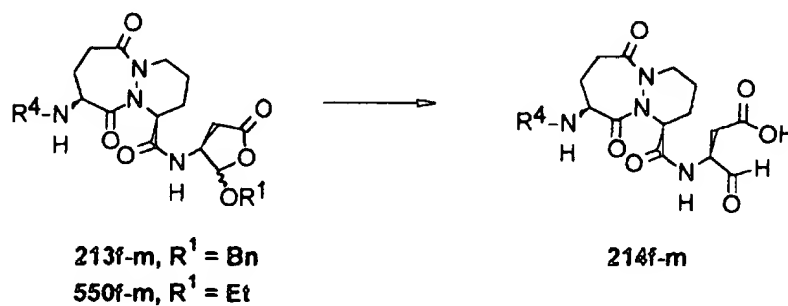
The hydrolysis may be carried out under various conditions, provided that the conditions include an acid and H₂O. Acids that may be used include p-toluensulfonic, methanesulfonic acid, sulfuric, perchloric, trifluoroacetic, and hydrochloric. For example, trifluoroacetic acid (1-90% by weight) or

- 551 -

hydrochloric acid (0.1-30% by weight) in CH₃CN/H₂O
(1-90% H₂O by weight) at between 0-50 °C may be used.

Example 29

Compounds 213f, 213g, 213h, 213i, 213j, 213k,
5 213l, 213m, 214f, 214g, 214h, 214i, 214j, 214k, 214l,
214m, 550f, 550g, 550h, 550i, 550j, 550k, 550l and 550m
were prepared as follows.



[1*S*, 9*S*(2*RS*, 3*S*)] 9-[(4-Dimethylaminobenzoyl)amino]-6,10-
dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-Benzoyloxy-5-
10 oxotetrahydrofuran-3-yl)-6*H*-
pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (213f),
was synthesized from 212f by the methods used to

- 552 -

prepare **213e** from **212e** to afford 504 mg of **213f** as a yellow solid, ¹H NMR (CD₃OD) δ 1.10(br. m, 0.25H), 1.30(br. m, 2H), 1.50(br. m, 1H), 1.65(br. m, 1.5H), 1.80(br. m, 0.25H), 1.90(br. m, 0.25H), 1.95(br. m, 0.5H), 2.05(br. m, 0.25H), 2.15(m, 1H), 2.3(m, 1H), 2.5(br. m, 1H), 2.6(dd, 1H), 2.8(m, 1H), 3.1(br. s, 3H), 3.15(br. m, 1H), 3.32(br. s, 3H), 3.5(m, 1H), 4.5(br. m, 1H), 4.62(d, 0.25H), 4.72(m, 3H), 4.95(m, 1H), 5.1(br. t, 0.25H), 5.15(br. t, 0.75H), 5.7(d, 1H), 6.75(d, 2H), 7.35(br. s, 5H), 7.75(d, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213g**),
was synthesized from **212g** by the methods used to prepare **213e** from **212e** to afford 400 mg of **213g**, ¹H NMR (CD₃OD) δ 1.5(br. m, 1H), 1.65(br. m, 2H), 1.70(br. m, 0.25H), 1.90(br. m, 1H), 1.95(br. m, 1H), 2.05(br. m, 0.25H), 2.10(m, 1H), 2.3(m, 1H), 2.5(m, 2H), 2.59(d, 1H), 2.6(d, 1H), 2.78(d, 1H), 2.8(d, 1H), 2.93(br. s, 4H), 3.05(br. m, 1H), 3.15(br. m, 0.25H), 3.3(br. s, 3H), 3.5(m, 2H), 4.5(br. m, 2H), 4.65(d, 1H), 4.7(br. m, 2H), 4.95(br. m, 1H), 5.15(br. t, 0.25H), 5.2(br. t, 0.75H), 5.2(d, 1H), 6.95(d, 1H), 7.15(d, 1H), 7.25(br. s, 1H), 7.3(br. t, 2H), 7.45(br. s, 6H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213h**),
was synthesized from **212h** by the methods used to

- 553 -

prepare 213e from 212e to afford 296 mg of 213h, ¹H NMR (CDCl₃) δ 1.55-1.68(m, 1H), 1.7-2.05(m, 3H), 2.3-2.5(m, 2H), 2.65-2.8(m, 1H), 2.85-2.93(m, 1H), 2.95-3.25(m, 3H), 4.44-4.65(m, 2H), 4.68-4.82(m, 1H), 4.9-4.95(d, 1H), 5.05-5.18(m, 2H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.52-6.58(d, 0.5H), 6.7-6.76(m, 2H), 6.82-6.85(d, 0.5H), 7.3-7.4(m, 5H), 7.52-7.58(m, 1H), 7.75(s, 0.5H), 7.8(s, 0.5H).

[1S,9S(2RS,3S)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213i), was synthesized from 212i by the methods used to prepare 213e from 212e to afford 1.1 g of 213i, ¹H NMR (CDCl₃) δ 1.55-2.05(m, 6H), 2.26-2.5(m, 2H), 2.68-2.82(m, 1H), 2.85-2.92(m, 1H), 2.95-3.25(m, 2H), 3.82(s, 1.5H), 3.85(s, 1.5H), 4.4-4.65(m, 2H), 4.7-4.78(m, 1H), 4.88-4.95(m, 1H), 5.05-5.23(m, 1H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.6-6.65(m, 1H), 6.8-6.84(m, 1H), 6.9-6.95(m, 3H), 7.3-7.45(m, 4H), 7.78-7.85(m, 2H).

[1S,9S(2RS,3S)]9-[(3,5-Dichlorobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213j), was synthesized from 212j by the methods used to prepare 213e from 212e to afford 367 mg of 213j, ¹H NMR (CDCl₃) δ 1.55-2.05(m, 12H), 2.25(d, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.75(m, 2H), 2.9(m, 1H), 2.95-3.25(m, 5H), 4.45(t, 1H), 4.5-4.6(m, 4H), 4.7(m, 1H), 4.75(d, 1H),

- 554 -

4.88(m, 1H), 5.05(m, 2H), 5.15(q, 1H), 5.3(s, 1H),
5.58(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 7.05(d, 1H), 7.25-
7.35(m, 5H), 7.6(s, 2H), 7.7(s, 2H).

- [1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-
5 hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-
octahydro-*N*-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6*H*-
pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (213*k*),
was synthesized from 212*k* by the methods used to
prepare 213*e* from 212*e* to afford 593 mg of 213*k*, ¹H NMR
10 (CD₃OD) δ 1.5(m, 1H), 1.6-1.7(m, 2H), 1.75-1.95(m, 4H),
2.15(m, 2H), 2.3(m, 1H), 2.6(m, 1H), 2.7(m, 1H),
3.05(m, 2H), 3.15(m, 1H), 3.5(m, 2H), 4.45(m, 2H),
4.65(d, 1H), 4.7(m, 1H), 4.95(m, 1H), 5.15(m, 1H),
5.4(s, 1H), 5.7(d, 1H), 7.3(m, 5H), 7.85(s, 2H).
- 15 [1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-
6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-Benzyloxy-5-
oxotetrahydrofuran-3-yl)-6*H*-
pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (213*l*),
was synthesized from 212*l* by the methods used to
20 prepare 213*e* from 212*e* to afford 133 mg of 213*l*, ¹H NMR
(CDCl₃) δ 1.55-1.7(m, 1H), 1.75-2.05(m, 3H), 2.25(s,
1.5H), 2.27(s, 1.5H), 2.3-2.48(m, 2H), 2.7-2.83(m, 1H),
2.85-2.94(dd, 1H), 2.95-3.25(m, 2H), 4.42-4.65(m, 2H),
4.68-4.85(m, 1H), 4.88-4.95(m, 1H), 5.05-5.18(m, 2H),
25 5.32(s, 0.5H), 5.55-5.6(d, 0.5H), 6.48-6.55(d, 1H),
6.88-6.92(d, 1H), 7.0-7.04(d, 0.5H), 7.15-7.2(d, 0.5H),
7.3-7.4(m, 4H), 7.64-7.78(m, 2H), 7.88-7.94(m, 1H),
8.45-8.56(m, 1H).
- [1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-
30 methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-

- 555 -

octahydro-N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213m), was synthesized from 212m by the methods used to prepare 213e from 212e to afford 991 mg of 213m, ¹H NMR

5 (CDCl₃) δ 1.5-2.15(m, 5H), 2.2-2.55(m, 3H), 2.6-3.3(m, 4H), 3.95(2s, 3H), 4.45-4.7(m, 2H), 4.7-4.85(m, 1H), 4.85-4.95(m, 1H), 5.05-5.25(m, 1H), 5.3(s, 0.5H), 5.6(d, 0.5H), 6.55(d, 0.5H), 6.85(d, 0.5H), 7.0(d, 0.5H), 7.25-7.6(m, 5.5H), 7.75(s, 1H), 7.85(s, 1H).

10 [1S,9S(2RS,3S)]9-[(4-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-

pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550f), was synthesized from 212f by the methods used to

15 prepare 213e from 212e to afford 420 mg of 550f as an off white solid, ¹H NMR (CDCl₃) δ 1.2-1.25(br. t, 3H), 1.35(m, 1H), 1.55(br. m, 1H), 1.88-2.02(br. m, 4H), 2.3(d, 1H), 2.35(m, 1H), 2.45(m, 1H), 2.55-2.75(m, 3H), 3.0(s, 6H), 3.25(m, 1H), 3.55(m, 1H), 3.65(m, 1H),
20 3.75(m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 4.95(br. m, 1H), 5.1(br. m, 2H), 5.45(d, 1H), 6.5(m, 2H), 7.7(m, 2H).

[1S,9S(2RS,3S)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-

pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550h), was synthesized from 212h by the methods used to prepare 213e from 212e to afford 195 mg of 550h as a

30 white solid, ¹H NMR (DMSO-d₆) δ 1.1-1.18(2t, 3H), 1.6-

- 556 -

1.7(m, 2H), 1.88-2.05(m, 2H), 2.1-2.35(m, 3H), 2.48-2.56(m, 1H), 2.75-2.8(m, 0.75H), 2.88-3.08(m, 1.25H), 3.25-3.4(m, 1H), 3.55-3.8(m, 2H), 4.35-4.45(m, 1H), 4.55-4.62(m, 1H), 4.8-4.88(m, 1H), 4.98-5.03(m, 0.25H),
5 5.1-5.13(m, 0.75H), 5.33(s, 0.25H), 5.58-5.6(d, 0.75H), 5.9-6.0(br. s, 2H), 6.8-6.85(d, 1H), 7.58-7.62(d, 1H), 7.82(s, 1H), 8.22-8.28(d, 1H), 8.48-8.52(d, 0.75H), 8.72-8.76(d, 0.25H).

[1*S*, 9*S*(2*RS*, 3*S*)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-
10 1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550i),
was synthesized from 212i by the methods used to prepare 213e from 212e to afford 135 mg of 550i, ¹H NMR
15 (CDCl₃) δ 1.18-1.28(2t, 3H), 1.6-1.75(m, 1.5H), 1.9-2.1(m, 3.5H), 2.22-2.3(d, 0.5H), 2.38-2.47(m, 1.5H), 2.7-2.8(m, 0.5H), 2.8-2.93(m, 1H), 2.94-3.15(m, 1.5H), 3.15-3.28(m, 1H), 3.55-3.62(q, 0.5H), 3.62-3.73(q, 0.5H), 3.78-3.88(q, 0.5H), 3.88(s, 3H), 3.9-3.95(q, 0.5H), 4.33-4.4(m, 0.5H), 4.5-4.55(m, 1H), 4.68-4.76(m, 0.5H), 4.9-4.95(m, 0.5H), 5.1-5.2(m, 1.5H), 5.18(s, 0.5H), 5.48-5.52(d, 0.5H), 6.48-6.55(d, 0.5H), 6.85-6.9(m, 1H), 6.9-6.95(m, 2H), 7.34-7.38(d, 0.5H), 7.78-7.85(m, 2H).

25 [1*S*, 9*S*(2*RS*, 3*S*)]9-[(3,5-Dichloro-4-hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550k),
was synthesized from 212k by the methods used to
30 prepare 213e from 212e to afford 174 mg of 550k as a white solid, ¹H NMR (DMSO-d₆) δ 1.15(2t, 3H), 1.6-

- 557 -

1.75(m, 2H), 1.9-2.05(m, 2H), 2.1-2.4(m, 5H), 2.5-2.55(m, 1H), 2.7-2.8(m, 0.5H), 2.85-3.0(m, 1H), 3.0-3.1(m, 0.5H), 3.55-3.7(m, 1H), 3.7-3.8(m, 1H), 4.2(t, 0.5H), 4.35-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.8-4.9(m, 0.5H), 5.05(t, 0.5H), 5.15(t, 0.5H), 5.35(s, 0.5H), 5.6(d, 0.5H), 7.95(s, 2H), 8.5(d, 0.5H), 8.65(d, 1H), 8.75(d, 0.5H), 10.9(br. s, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (5501), was synthesized from 2121 by the methods used to prepare 213e from 212e to afford 151 mg of 5501, ¹H NMR (CDCl₃) δ 1.2-1.28(2t, 3H), 1.6-1.72(m, 1.5H), 1.88-2.15(m, 3.5H), 2.22-2.28(m, 0.5H), 2.28(s, 3H), 2.38-2.48(m, 1.5H), 2.66-2.92(m, 1.5H), 2.95-3.14(m, 1.5H), 3.2-3.34(m, 1H), 3.56-3.63(q, 0.5H), 3.63-3.72(q, 0.5H), 3.8-3.85(q, 0.5H), 3.9-3.95(q, 0.5H), 4.32-4.38(m, 0.5H), 4.5-4.62(m, 1H), 4.68-4.75(m, 0.5H), 4.88-4.92(m, 0.5H), 5.08-5.2(m, 1.5H), 5.18(s, 0.5H), 5.46-5.5(d, 0.5H), 6.5-6.55(d, 0.5H), 6.98-7.05(m, 1H), 7.42-7.48(d, 0.5H), 7.63-7.78(m, 2.5H), 7.9-7.94(d, 0.5H), 8.44-8.52(m, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (550m), was synthesized from 212m by the methods used to prepare 213e from 212e to afford 301 mg of 550m as a white solid, ¹H NMR (CDCl₃) δ 1.2-1.35(2t, 3H), 1.5-

- 558 -

1.8(m, 2H), 1.9-2.15(5H), 2.25(d, 0.5H), 2.4-2.5(m, 2H), 2.65-2.8(m, 0.5H), 2.8-3.0(m, 0.5H), 3.0-3.2(m, 1H), 3.2-3.35(m, 0.5H), 3.55-3.65(m, 0.5H), 3.65-3.75(m, 0.5H), 3.8-3.9(m, 0.5H), 3.9-4.0(m, 0.5H), 4.4-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.7-4.8(m, 0.5H), 4.85-4.95(m, 0.5H), 5.05-5.2(m, 0.5H), 5.2(s, 0.5H), 5.5(d, 0.5H), 6.5(d, 0.5H), 6.9(d, 0.5H), 6.95(d, 0.5H), 7.35(d, 0.5H), 7.75(s, 1H), 7.85(s, 1H).

[3S(1S,9S)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214j), was synthesized from 213j by the method used to prepare 2002 from 2001 to afford 62 mg of 214j as a white solid, ¹H NMR (CD₃OD) δ 0.9 (t, 1H), 1.3(br. s, 1H), 1.7(br. m, 1H), 1.9(br. m, 1H), 2.1(br. s, 1H), 2.25(q, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.65(t, 1H), 3.15(br. t, 1H), 3.5(br. m, 1H), 4.3(br. s, 1H), 4.55(m, 2H), 4.95(t, 1H), 5.25(br. s, 1H), 7.6(br. s, 1H), 7.85(br. s, 1H).

[3S(1S,9S)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214k), was synthesized from 213k by the method used to prepare 2002 from 2001 to afford 80 mg of 214k as a white solid, ¹H NMR (CD₃OD) δ 1.6-1.7(m, 1H), 1.8-2.0(m, 2H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.4-2.55(m, 2H), 2.6-2.75(m, 1H), 3.05-3.2(m, 1H), 3.4-3.6(m, 2H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.8-5.0(m, 1H), 5.1-5.2(m, 1H), 7.85(s, 2H).

- 559 -

[3S(1S,9S)]3-(9-(3-Chloro-4-acetamidobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214l), was synthesized from 213l by

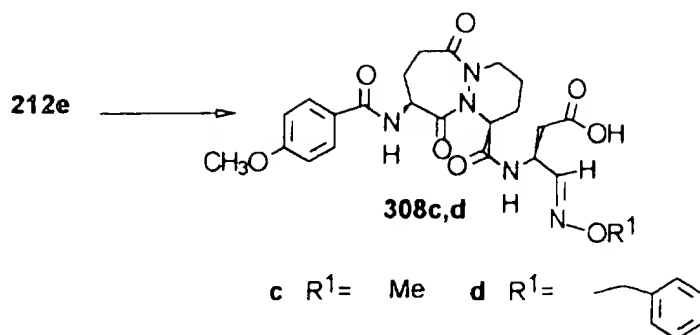
5 the method used to prepare 2002 from 2001 to afford 91 mg of 214l as a white solid, ¹H NMR (DMSO-d₆) δ 1.65(br. m, 6H), 1.9(br. m, 6H), 2.15(s, 3H), 2.3(m, 3H), 2.6-2.85(m, 3H), 2.9(m, 2H), 3.0(m, 1H), 4.15(br. q, 1H), 4.4(m, 3H), 5.0(m, 1H), 5.15(m, 1H), 5.45(s, 1H),
10 7.8(d, 2H), 7.95(d, 1H), 8.05(s, 1H), 8.65(m, 2H), 9.65(s, 1H).

[3S(1S,9S)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-

15 oxobutanoic acid (214m), was synthesized from 213m by the method used to prepare 2002 from 2001 to afford 105 mg of 214m as a white solid, ¹H NMR (CD₃OD) δ 1.6-1.75(m, 1H), 1.85-1.95(m, 1H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.45-2.55(m, 2H), 2.65-
20 2.75(m, 1H), 3.4-3.55(m, 2H), 3.95(s, 3H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.9-5.0(m, 1H), 5.15-5.2(m, 1H), 7.9(s, 2H).

Compounds 308c and 308d were prepared as follows.

- 560 -



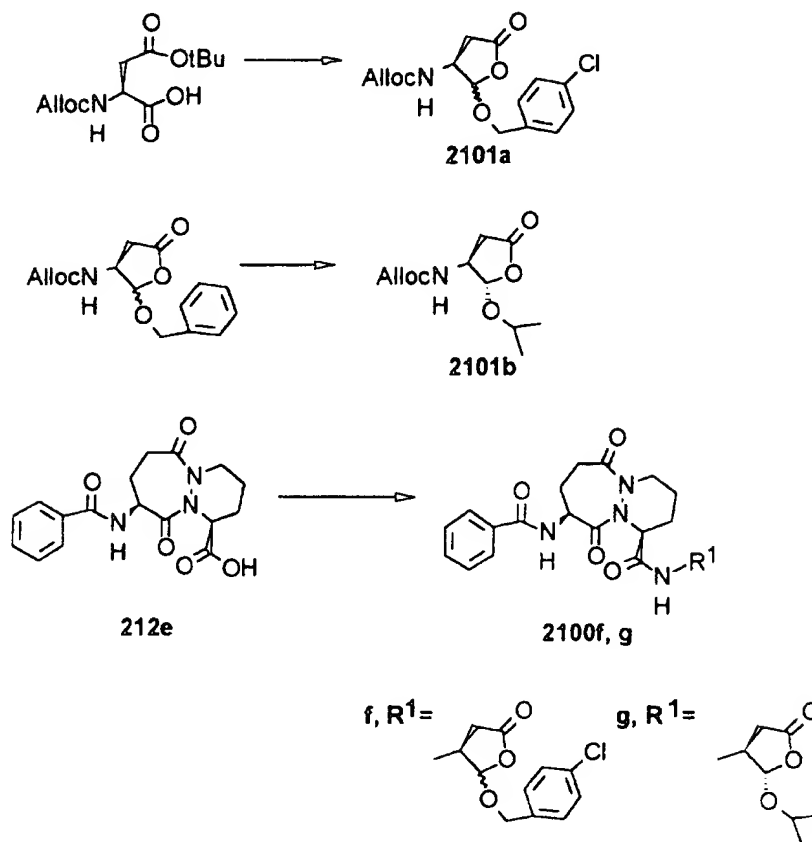
[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-6H-
 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-amino]-
 4-oxobutanoic acid, O-methyl oxime (308c), was
 5 synthesized from 212e via the methods used to prepare
 308b from 212e to afford 266 mg of 308c ¹H NMR (CDCl₃) δ
 1.6-1.7(m, 1H), 1.88-1.98(m, 3H), 2.02-2.15(m, 1H),
 2.3-2.4(m, 1H), 2.65-2.95(m, 3H), 3.04-3.09(m, 1H),
 3.12-3.25(m, 1H), 3.84(s, 3H), 3.86(s, 3H), 4.5-4.58(m,
 10 1H), 4.88-4.95(m, 1H), 5.1-5.25(m, 2H), 6.86-6.9(d,
 2H), 7.15-7.25(m, 2H), 7.36-7.4(m, 1H), 7.75-7.8(d,
 2H).

[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-6H-
 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-amino]-
 4-oxobutanoic acid, O-benzyl oxime (308d), was
 15 synthesized from 212e via the methods used to prepare
 308b from 212e to afford 270 mg of 308d, ¹H NMR (CDCl₃)
 δ 1.55-1.65(m, 1H), 1.8-2.1(m, 4H), 2.3-2.4(m, 1H),
 20 2.65-2.88(m, 3H), 2.9-3.3(m, 3H), 4.5-4.58(m, 1H),
 4.88-4.95(m, 1H), 5.05(s, 2H), 5.1-5.2(m, 1H), 6.82-

- 561 -

6.95 (m, 2H), 7.02-7.15 (m, 2H), 7.28 (m, 5H), 7.45 (m, 1H), 7.72 (d, 2H).

Compounds 2100f, 2100g, 2100h, 2100i and 2100j were prepared as described below.



5 (3*S*,2*RS*) 3-Allyloxycarbonylamino-2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran (2101a), was synthesized from allyloxycarbonylamino- β -tert-butyl aspartate by the methods employed by Chapman (Bioorg. & Med. Chem. Lett., 2, pp.615-618 (1992)) to prepare (3*S*,2*RS*; 3-
10 allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran

- 562 -

using 4-chlorobenzyl alcohol instead of benzyl alcohol to afford 1.84 g of 2101a as a crystalline solid.

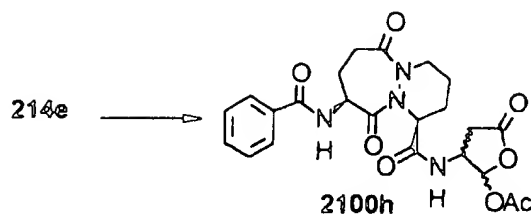
[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100f), was synthesized from 212e by the methods used to prepare 213e from 212e using 2101a to afford 380 mg of 2100f, ¹H NMR (CDCl₃) δ 1.8-2.0(m, 10H), 2.30(d, 1H), 2.31-2.5(m, 3H), 2.7-2.9(m, 3H), 3.05(m, 2H), 3.1-3.2(m, 4H), 4.45(q, 1H), 4.5-4.6(m, 3H), 4.7(d, 2H), 4.85(d, 1H), 4.9(t, 1H), 5.2(t, 1H), 5.15(m, 2H), 5.25(s, 1H), 5.55(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 6.95(d, 1H), 7.25(m, 3H), 7.35(t, 2H), 7.45(m, 2H), 7.55(1H), 7.8(m, 3H).

(3*S*,2*RS*) 3-Allyloxycarbonylamino-2-anti-isopropoxy-5-oxotetrahydrofuran (2101b), was synthesized from (3*S*,2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran via the method used to prepare 2100d from 214e using H₂SO₄ instead of pTSA to afford 2101b.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-anti-isopropoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100g), was synthesized from 212e by the methods used to prepare 213e from 212e using 2101b to afford 31 mg of 2100g, ¹H NMR (CDCl₃) δ 1.19 (d), 1.94 (br s), 2.00-2.12 (m), 2.24 (d), 2.42 (dd), 2.71-2.83 (m), 3.02 (dd), 3.12-3.27 (overlapping m), 3.93 (m), 4.32-4.37 (m),

- 563 -

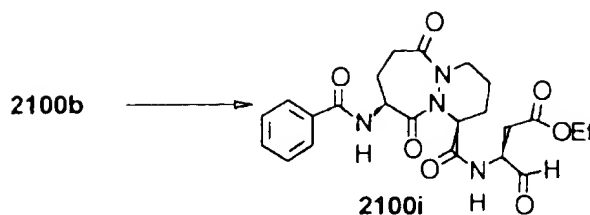
4.52-4.63 (m), 4.90-4.95 (m), 5.12-5.20 (m), 5.28 (s),
6.93 (d), 7.10 (d), 7.41-7.50 (m), 7.51-7.58 (m), 7.84
(d).



[1*S*,9*S*(2*RS*,3*RS*)] 9-Benzoylamino-6,10-dioxo-
5 1,2,3,4,7,8,9,10-octahydro-*N*-(2-acetoxy-5-oxotetrahydrofuran-3-yl)-6*H*-
pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (2100h).

A solution of 214e (287 mg, 0.65 mmol) in pyridine (5 mL) was treated with Ac₂O (0.4 mL, 3.62 mmol). After 6
10 hours, the reaction mixture was poured into 5% NaHSO₄ and extracted 3 times with EtOAc. The combined organics were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Chromatography (SiO₂, EtOAc) afforded 119 mg of 2100h, ¹HNMR (CDCl₃, mixture of four
15 diastereoisomers) δ 1.80-2.05(m), 2.12(s), 2.13(s), 2.19(s), 2.22(d), 2.67-2.75(m), 2.80-2.95(m), 3.00-3.20(m), 3.21-3.33(m), 3.50-3.95(four discrete multiplets), 4.19(m), 4.55(m), 4.57-4.65(m), 4.69(m), 4.85-4.95(m), 5.04(m), 5.10(s), 5.10-5.22(m), 6.46(d),
20 6.03(s), 6.50(d), 6.58(d), 6.75(d), 6.95-7.05(m), 7.22(m), 7.30(m), 7.71(d), 7.75-7.83(m).

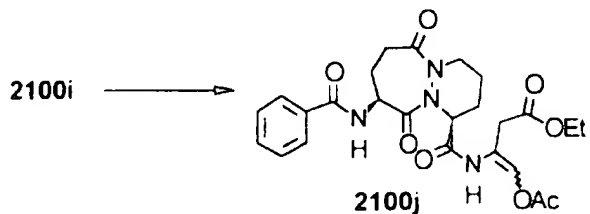
- 564 -



[3*S*(1*S*,9*S*)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid ethyl ester (2100i). To a solution of

5 2100b (1.5 g, 2.7 mmol) in CH₃CN (10 mL) was added 1*N* HCl at ambient temperature. After 6 hours solid NaHCO₃ was added and the product extracted with EtOAc, dried over MgSO₄ and concentrated *in vacuo*. Chromatography (SiO₂, 30-100% CH₂Cl₂ in EtOAc) afforded 123 mg of

10 2100i, ¹H NMR (CDCl₃) δ 1.25(t, 3H), 1.6-1.8(m, 1H), 1.9-2.2(m, 5H), 2.4-2.5(m, 1H), 2.75-2.9(m, 2H), 3.0-3.1(m, 2H), 3.2-3.25(m, 1H), 4.05-4.2(m, 1H), 4.5-4.7(m, 1H), 5.1-5.25(m, 1H), 7.0-7.2(m, 2H), 7.4-7.45(m, 2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).



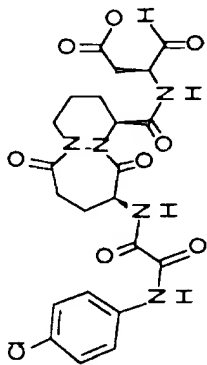
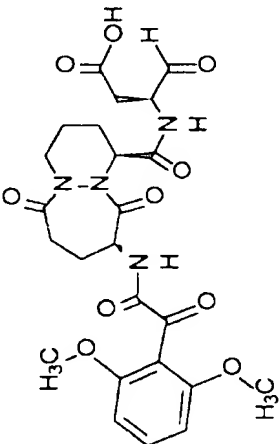
15 [3*S*(1*S*,9*S*)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-acetoxy-3-butenic acid ethyl ester (2100j), was synthesized from 2100i via the method used to prepare

- 565 -

2100h from 214e to afford 347 mg of 2100j, ¹H NMR
(CDCl₃) δ 1.3(t, 3H), 1.6-1.8(m, 2H), 1.9-2.25(m, 4H),
2.25(s, 3H), 2.3-2.45(m, 1H), 2.8-3.0(m, 1H), 3.0-
3.25(m, 2H), 3.4-3.45(m, 2H), 4.1-4.2(m, 2H), 4.55-
5 4.7(m, 1H), 5.1-5.25(m, 1H), 6.8(s, 1H), 7.0-7.1(m,
2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).

Compounds 500 and 501 are described in Table
23. These compounds were prepared by methods similar
to the methods used to prepare compounds 404-449 (see,
10 Example 11).

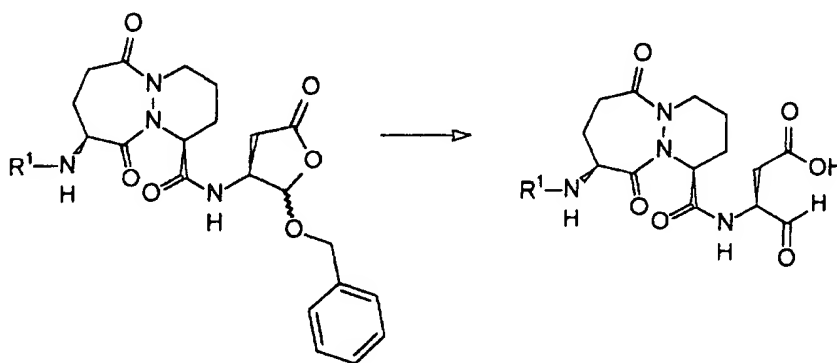
Table 23

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+H) ⁺
500		C22H24ClN5O8	521.92	11.448 (A) 0.991	523.1
501		C24H28N4O10	532.51	10.13 0.97	533

- 567 -

The compounds described below (213m, 213n, 213o, 213p, 213q, 213r, 213s, 213t, 213u, 213v, 213w, 213x, and 214w), were prepared by methods similar to the methods used to prepare compounds 213b-f.

5 Compounds 419, 415, 450, 456, 475, 404, 486, 487, 417, 408 and 418 may also be prepared as described below.



213m-x
214w, 404, 408, 415,

10

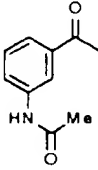
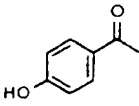
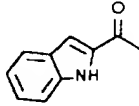

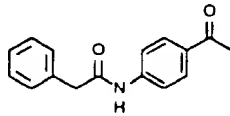
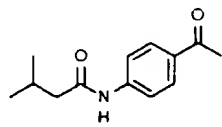
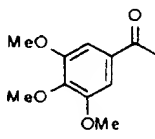
417, 418, 419, 450,

15

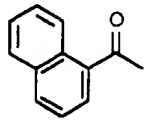
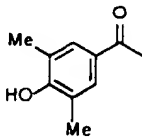
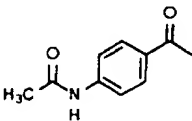
456, 475, 486, 487

compound	R ¹
213m, 419	MeOC(O)-
213n, 415	

- 568 -

213o, 450	 <chem>CC(=O)Nc1ccc(C(C)=O)cc1</chem>
213p, 456	 <chem>CC(=O)c1ccc(O)cc1</chem>
213q, 475	 <chem>CC(=O)c1c[nH]c2ccccc12</chem>
213r, 404	 <chem>CC(=O)c1ccccc1C</chem>
213s, 486	 <chem>CC(=O)c1ccc(NC(=O)Cc2ccccc2)cc1</chem>
213t, 487	 <chem>CC(=O)c1ccc(NC(=O)CC(C)C)cc1</chem>
213u, 417	 <chem>CC(=O)c1cc(OC)c(OC)c(C(=O)O)c1</chem>

- 569 -

213v, 408	
213w, 214w	
213x, 418	

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213n),
 5 was isolated as a mixture of diastereomers (syn:anti isomer ratio 6:4) (1.43g, 82%) as a white solid: mp. 206-10°C; IR (KBr) 3288, 1787, 1680, 1657, 1651, 1619, 1548, 1440, 1256, 1135; ¹H NMR (D₆-DMSO) δ 8.75 (0.4H, d), 8.55 (0.6H, d), 8.45 and 8.43 (1H, 2 x d), 7.50 (1H, d), 7.42 (1H, s), 7.40-7.27 (5H, m), 7.01 (1H, d), 6.11 (2H, s), 5.67 (0.6H, d), 5.43 (0.4H, s), 5.10-5.00
 10 (1H, m), 4.90-4.59 (3.5H, m), 4.45-4.25 (1.5H, m), 3.47-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.35 (1H, m), 2.35-2.00 (3H, m), 2.00-1.75 (2H, m), 1.65-1.40 (2H, m). Anal. Calcd for C₂₉H₃₀N₄O₉: C, 60.20; H, 5.23; N, 9.68. Found: C, 60.08; H, 5.32; N, 9.50. MS (ES⁺)

- 570 -

580 ($M^+ + 2$, 35%), 579 ($M^+ + 1$, 100), 404 (5), 367 (5),
236 (7), 107 (5).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-
5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213o),
anti-isomer as a white foamy solid (0.73g, 69%): mp.
135-40°C; $[\alpha]_D^{21}$ -37.3° (c 0.1, CH₂Cl₂); IR (KBr) 3452,
3310, 1790, 1664, 1659, 1650, 1549, 1425, 1258, 1121;
10 ¹H NMR (D₆-DMSO) δ 10.11 (1H, s), 8.77 (1H, d), 8.57
(1H, d), 8.01 (1H, s), 7.76 (1H, d), 7.55 (1H, d),
7.45-7.25 (6H, m), 5.43 (1H, s), 5.08-5.00 (1H, m),
4.95-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20
(1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.45-2.06
15 (4H, m), 2.06 (3H, s), 2.00-1.75 (2H, m), 1.70-1.40
(2H, m). Anal. Calcd for C₃₀H₃₃N₅O₈•0.75H₂O: C, 59.54;
H, 5.75; N, 11.57. Found: C, 59.40; H, 5.62; N, 11.50.
MS (ES⁺) 593 ($M^+ + 2$, 33%), 592 ($M^+ + 1$, 100), 574 (7),
487 (7), 475 (6), 385 (9), 373 (26), 318 (14), 296
20 (11), 266 (10), 221 (22).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxybenzoyl)amino-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213p),
25 was isolated as a foam (1.2g, 77%): $[\alpha]_D^{20}$ -115° (c
0.20, CH₂Cl₂); IR (KBr) 3368, 2946, 1794, 1654, 1609,
1540, 1505, 1421, 1277, 1175, 1119, 980; ¹H NMR (D₆-
DMSO) δ 10.1 (1H, s), 8.80 (0.5H, d, J = 6.6), 8.60
(0.5H, d, J = 7.2), 8.40-8.36 (1H, 2d), 7.82 (2H, d, J
30 = 8.0), 7.41 (5H, bs), 6.86 (2H, d, J 8.6), 5.72 (0.5H,

- 571 -

d, $J = 5.0$), 5.49 (0.5H, bs), 5.13-5.07 (1H, m), 4.95-4.65 (2.5H, m), 4.49-4.38 (2.5H, m), 3.49-3.30 (2H, m), 3.21, 2.79 (2H, m), 2.40-1.41 (7H, m). MS (ES^+) 551.

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213q), was isolated as a white glassy solid (80%): mp. 145-149°C; $[\alpha]_D^{23} -56.0^\circ$ (c 0.05, CH_2Cl_2); IR (KBr) 3399-3319, 1791, 1657, 1543, 1420, 1253, 1119; 1H NMR ($CDCl_3$) δ 9.54 (1H, s), 7.65 (1H, d, $J = 7.9$), 7.51 (1H, d, $J = 6.9$), 7.44-7.25 (7H, m), 7.18-7.06 (3H, m), 5.30-5.20 (1H, m), 5.27 (1H, s), 4.84 (1H, m), 4.79 (1H, d, $J = 11.4$), 4.56 (1H, d, $J = 11.3$), 4.47 (2H, m), 3.28 (1H, m), 3.10-2.97 (2H, m), 2.71 (1H, m), 2.47-2.37 (1H, m), 2.26 (1H, d, $J = 17.9$), 2.09 (1H, m), 1.83, 1.70, 1.51 (4H, 3m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213r), was isolated as a mixture of diastereomers (syn:anti isomer ratio 55:45) as a white foamy solid (1.46g, 89%): mp. 106-110°C; IR (KBr) 3306, 2947, 1791, 1659, 1650, 1535, 1421, 1256, 1122; 1H NMR (D_6 -DMSO) δ 8.76 (0.45H, d), 8.56 (0.55H, d), 8.49 and 8.47 (1H, 2 x d), 7.41-7.19 (9H, m), 5.67 (0.55H, d), 5.43 (0.45H, s), 5.11-5.02 (1H, m), 4.86-4.55 (3.5H, m), 4.45-4.25 (1.5H, m), 3.40-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.40 (1H, m), 2.34 (3H, s), 2.30-1.70 (5H, m), 1.65-1.40 (2H, m). Anal. Calcd for $C_{29}H_{32}N_4O_7$: C, 62.66; H, 5.95; N, 10.08. Found: C, 62.91; H, 6.00;

- 572 -

N, 9.70. MS (ES^+) 550 ($M^+ + 2$, 43%), 549 ($M^+ + 1$, 100), 374 (3), 280 (4), 279 (20), 118 (5).

[1S,9S(2RS,3S)]N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-

5 **(phenylacetamido)benzamido]-6H-**

pyridazino[1,2-a][1,2]diazepin-1-carboxamide (213s),

was isolated as the anti-isomer as a white foamy solid

(0.64g, 77%): mp. 137-41°C; $[\alpha]_D^{21}$ -48.2° (c 0.05,

CH₃OH); IR (KBr) 3477, 3314, 1791, 1659, 1599, 1529,

10 1499, 1406, 1256, 1122; ¹H NMR (D₆-DMSO) δ 10.45 (1H, s), 8.76 (1H, d), 8.50 (1H, d), 7.86 (2H, d), 7.69 (2H, d), 7.41-7.20 (10H, m), 5.43 (1H, s), 5.08-4.98 (1H, m), 4.90-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.67

(2H, s), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75

15 (1H, m), 2.39 (1H, dd), 2.30-2.00 (3H, m), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m). Anal. Calcd for

C₃₆H₃₇N₅O₈•0.5H₂O: C, 63.90; H, 5.66; N, 10.35. Found:

C, 63.68; H, 5.67; N, 10.24. MS (ES^+) 669 ($M^+ + 2$, 40%), 668 ($M^+ + 1$, 100), 640 (12), 435 (18), 425 (23),

20 403 (33), 328 (17), 302, (32), 274 (22), 197 (16), 138 (17).

[1S,9S(2RS,3S)]N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-[4-(3-methylbutan-1-

oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-

25 **pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213t),**

was isolated as a white foamy solid (0.63g, 80%); mp.

159-64°C; $[\alpha]_D^{21}$ -37.0° (c 0.05, CH₃OH); IR (KBr) 3463,

3321, 1790, 1680, 1658, 1650, 1644, 1595, 1525, 1501,

1408, 1251, 1113, 933; ¹H NMR (D₆-DMSO) δ 10.13 (1H, s),

30 8.76 (1H, d), 8.48 (1H, d), 7.85 (2H, d), 7.68 (2H, d),

- 573 -

7.40-7.25 (5H, m), 5.43 (1H, s), 5.08-4.95 (1H, m),
 4.92-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20
 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.39 (1H,
 dd), 2.35-2.00 (6H, m), 2.00-1.75 (2H, m), 1.70-1.40
 5 (2H, m), 0.93 (6H, d). Anal. Calcd for
 $C_{33}H_{39}N_5O_8 \cdot 0.5H_2O$: C, 61.67; H, 6.27; N, 10.90. Found:
 C, 61.49; H, 6.24; N, 10.86. MS (ES^+) 635 ($M^+ + 2$,
 39%), 634 ($M^+ + 1$, 100), 484 (10), 427 (9), 274 (18),
 268 (37), 204 (19), 117 (13).

10 **[1S,9S(2RS,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-trimethoxybenzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213u)**,
 was isolated as a white solid (81%): mp. 120-132°C; IR
 15 (KBr) 3361-3334, 1792, 1659, 1585, 1536, 1499, 1457,
 1416, 1340, 1236, 1126, 989; 1H NMR ($CDCl_3$) δ 7.39-7.29
 (6H, m), 7.12 (1H, s), 7.03 (1H, s), 6.92, 6.83, 6.48
 (approx 3H, 3d, $J = 8.1, 7.5, 8.1$), 5.57 (d, $J = 5.3$),
 5.27 (1H, s), 5.23-5.06, 4.91-4.71, 4.64-4.43, (6H,
 20 3m), 3.92, 3.91, 3.89, 3.88 (9H, 4s), 3.32-2.70, 2.52-
 2.08, 1.91, 1.63 (1H, 4m).

[1S,9S(2RS,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-
 25 **carboxamide (213v)**, was isolated as a white solid
 (78%): mp. 121-7°C; IR (KBr) 3534-3331, 1791, 1659,
 1528, 1420, 1256, 1122; 1H NMR ($CDCl_3$) δ 8.34-8.29 (1H,
 m), 7.98-7.87 (2H, m), 7.66-7.45 (4H, m), 7.34-7.24
 (5H, m), 7.04 (d, $J = 6.8$), 6.78 (d, $J = 7.8$), 6.66 (d,
 30 $J = 7.7$), 6.48 (2H, d, $J = 7.5$) 5.56 (d, $J = 5.4$), 5.15

- 574 -

(1H, s), 5.30-5.14, 5.0, 4.89 (d, J = 11.2), 4.71-4.41 (6H), 3.18-2.80, 2.50-2.27, 2.08-1.60 (11H, 3m).

[1S,9S(2RS,3S)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxy-3,5-dimethylbenzoyl)amino-
 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213w),
 was isolated as a mixture of diastereoisomers (65/35) as a white solid (0.9g, 65%): mp. 110-115°C (decomp.); IR (KBr) 3409, 2945, 1792, 1658, 1606, 1534, 1486,
 10 1420, 1330, 1276, 1209, 1122, 980, 960; ¹H NMR (CDCl₃) δ 7.66 (0.35H, d, J = 6.9), 7.46-7.20 (7H, m), 6.93 (0.35H, d, J = 7.7), 6.85 (0.65H, d, J = 7.6), 6.73 (0.65H, d, J = 7.6), 5.96 (0.35H, bs), 5.85 (0.65H, bs), 5.56 (0.65H, d, J = 5.2), 5.28 (0.35H, bs), 5.20-
 15 4.98 (2H, m), 4.96-4.40 (4H, m), 3.28-2.55 (3H, m), 2.53-2.32 (1H, m), 2.23 (6H, 2s), 2.03-1.40 (7H, m). MS (ES⁻) 577, (ES⁺) 579.

[1S,9S(2RS,3S)] 9-[4-(Acetylamino)benzoylamino]-N-(2-benzoyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-
 20 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboximide (213x),
 was isolated as a colourless powder (691mg, 86%): mp. 150-70°C; [α]_D²² -10.1° (c 0.10, Me₂CO); IR (KBr) 3313, 1791, 1679, 1654, 1597, 1528, 1501, 1457, 1407, 1371,
 25 1315, 1255, 1184, 1122, 933; ¹H NMR (d₆-DMSO) δ 8.75 (1H, d), 8.47 (1H, d), 7.84 (2H, d), 7.66 (2H, d), 7.35 (5H, m), 5.43 (1H, s), 5.06-5.00 (1H, m), 4.90-4.64 (3H, m), 4.46-4.26 (2H, m), 3.16-2.86 (2H, m), 2.45-2.05 (5H, m), 2.07 (3H, s), 2.00-1.84 (2H, m), 1.68-1.56 (2H, m);
 30 Anal. Calcd for C₃₀H₃₃N₅O₈·H₂O: C, 59.11; H, 5.79; N,

- 575 -

11.49. Found: C, 59.38; H, 5.66; N, 11.31; M.S. (ES⁺)
614 (100%), 592 (M⁺+1.66).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-
5 6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (415), was prepared by a similar method as compound 214e to afford a white solid (297mg, 84%): mp. 158-62°C; $[\alpha]_D^{24}$ -109.5° (c 0.1, CH₃OH); IR (KBr) 3700-2500 (br), 1783, 1659, 1650, 1538, 1486,
10 1439, 1257, 1037; ¹H NMR (CD₃OD) δ 7.48 (1H, dd), 7.35 (1H, d), 6.88 (1H, d), 6.03 (2H, s), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.63-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.05 (1H, m), 2.75-2.10 (5H, m), 2.10-1.60 (4H, m). MS (ES⁺) 488 (M⁺, 25%),
15 487 (M⁺ - 1, 100), 443 (8), 387 (3), 315 (5), 150 (6), 127 (5), 113 (8). Accurate mass calculated for C₂₂H₂₅N₄O₉ (MH⁺): 489.1621. Found 489.1648.

[3S(1S,9S)] 3-{9-[(3-Acetamido)benzamido]-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-
20 pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (450), was prepared by a similar method as compound 214e to afford a white foamy solid (378mg, 94%): mp. 175-9°C; $[\alpha]_D^{22}$ -91.7° (c 0.1, CH₃OH); IR (KBr) 3700-2500 (br), 3319, 1659, 1590, 1553, 1427,
25 1260; ¹H NMR (CD₃OD) δ 8.01 (1H, d), 7.74 (1H, dd), 7.56 (1H, d), 7.45-7.35 (1H, m), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-2.20 (5H, m), 2.14 (3H, s), 2.20-1.60 (4H). Anal. Calcd for
30 C₂₃H₂₇N₅O₈•1.5H₂O: C, 52.27; H, 5.72; N, 13.25. Found:

- 576 -

C, 52.31; H, 5.86; N, 12.85. MS (ES⁺) 501 (M⁺, 26%), 500 (M⁺ - 1, 100), 328 (2), 149 (3), 113 (3).

[3S(1S,9S)] 3-[4-(Hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-

5 pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (456), was prepared by a similar method as compound 214e to afford a white solid (0.73g, 72%): mp. >260°C; [α]_D²⁰ -66° (c 0.34, MeOH); IR (KBr) 3401, 2946, 1651, 1609, 1584, 1506, 1426, 1277, 1257,
10 1177; ¹H NMR (D₆-DMSO) δ 10.2 (1H, very bs), 9.17 (1H, bs), 8.65 (1H, s), 8.37 (1H, d, J 5.4), 7.81 (2H, d, J = 8.2), 6.87 (2H, d, J = 8.4), 5.24 (1H, m), 4.92-4.86 (1H, m), 4.41-4.32 (2H, m), 3.68-3.21 (3H, m), 3.12-2.79 (1H, m), 2.50-1.42 (7H, m). MS (ES⁺) 459.

15 [3S(1S,9S)] 3-[6,10-Dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (475), was prepared by a similar method to that described for compound 214e to afford a
20 white solid (79%): mp. 150°C (softens) 190-210°C; [α]_D²³ -97.5° (c 0.1, CH₃OH); IR (KBr) 3319, 1658, 1650, 1549, 1421, 1256; ¹H NMR (CD₃OD) δ 7.61 (1H, d, J = 8.0), 7.43 (1H, d, J = 8.1), 7.21 (2H, m), 7.05 (1H, m), 5.21 (1H, m), 5.07-4.77 (1H, m), 4.54 (2H, m), 4.23 (1H, m),
25 3.46 (1H, m), 3.14 (1H, m), 2.66-1.71 (9H, m). MS (ES⁺, m/z), 482 (M⁺ - 1, 100%).

[3S(1S,9S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (404), was prepared by

- 577 -

a similar method as compound **214e** to afford a white solid (0.79g, 86%): mp. 156-9°C; $[\alpha]_D^{25}$ -119.7° (c 0.1, CH₃OH); IR (KBr) 3700-2500 (br), 3387, 3309, 2956, 1785, 1659, 1650, 1535, 1422, 1278; ¹H NMR (CD₃OD) δ

5 7.46-7.15 (4H, m), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.58-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.05 (1H, m), 2.80-2.20 (4H, m), 2.41 (3H, s), 2.20-1.60 (5H, m). MS (ES⁺) 458 (M⁺, 27%), 457 (M⁺ - 1, 100), 413 (13), 339 (8), 285 (5), 134 (6),

10 127 (11). Accurate mass calculated for C₂₂H₂₇N₄O₇ (MH⁺): 459.1880. Found 459.1854.

[3S(1S,9S)] 3-{6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-(phenylacetamido)benzamido]-6H-pyridazino[1,2-a][1,2]

15 diazepine-1-carboxamido}-4-oxobutanoic acid (**486**), was prepared by a similar method as compound **214e** to afford a white solid (325mg, 89%): mp. 165-9°C; $[\alpha]_D^{22}$ -69.1° (c 0.1, CH₃OH); IR (KBr) 3700-2500 (br), 3318, 1658, 1599, 1530, 1505, 1407, 1258; ¹H NMR (CD₃OD) δ 7.85 (2H, d), 7.69 (2H, d), 7.38-7.20 (5H, m), 5.25-5.15 (1H, m),

20 5.05-4.90 (1H, m), 4.57-4.45 (2H, m), 4.30-4.20 (1H, m), 3.70 (2H, s), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (9H, m). Anal. Calcd for C₂₉H₃₁N₅O₈•1.5H₂O: C, 57.61; H, 5.67; N, 11.58. Found: C, 57.81; H, 5.74;

25 N, 11.47. MS (ES⁺) 577 (M⁺, 33%), 576 (M⁺ - 1, 100), 502 (2).

[3S(1S,9S)] 3-{6,10-Dioxo-9-[4-(3-methylbutan-1-oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-

30 oxobutanoic acid (**487**), was prepared by a similar

- 578 -

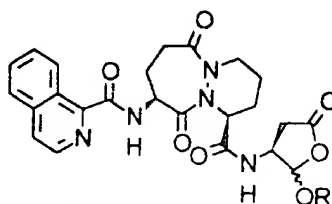
method as compound **214e** to afford a white foamy solid (335mg, 93%): mp. 176-80°C; $[\alpha]_D^{22}$ -88.0° (c0.1, CH₃OH); IR (KBr) 3700-2500 (br), 3321, 2960, 1781, 1660, 1597, 1529, 1407, 1258, 1187; ¹H NMR (CD₃OD) δ 7.86 (2H, d), 7.69 (2H, d), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (12H, m), 1.00 (6H, d). Anal. Calcd for C₂₆H₃₃N₅O₈•H₂O: C, 55.61; H, 6.28; N, 12.45. Found: C, 56.00; H, 6.37; N, 12.15. MS (ES⁺) 543 (M⁺, 31%), 542 (M⁺ - 1, 100), 498 (2), 468 (3).

[3S(1S,9S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-trimethoxybenzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (**417**), was prepared by a similar method to that described for compound **214e** to afford a white solid (0.63g, 92%): mp. 145-155°C (approx., not sharp); $[\alpha]_D^{27}$ -114.6° (c 0.11, CH₃OH); IR (KBr) 3327, 1658, 1586, 1548, 1501, 1416, 1341, 1238, 1126; ¹H NMR (CD₃OD) δ 7.22 (2H, s), 5.21 (1H, m), 5.00 (1H, m), 4.56, 4.49 (2H, 2m), 4.25 (1H, m), 3.88 (6H, s), 3.80 (3H, s), 3.55-3.43 (1H, m), 3.12 (1H, m), 2.71-1.70 (9H, m). Anal. Calcd for C₂₄H₃₀N₄O₁₀•2H₂O: C, 50.52; H, 6.01; N, 9.82. Found: C, 50.49; H, 6.05; N, 9.68. MS (ES⁺, m/z) 533 (M⁺ - 1, 100%).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (**408**), was prepared by a similar method to that described for compound **214e** to afford a

- 579 -

- white solid (73%): mp. 157-165°C (not sharp); $[\alpha]_D^{27}$ -140.5° (c 0.1, CH₃OH); IR (KBr) 3325, 1658, 1531, 1420, 1278, 1257; ¹H NMR (CD₃OD) δ 8.33-8.28 (1H, m), 8.01-7.78 (2H, m), 7.71 (1H, d, J = 6.0), 7.59-7.52 (3H, m), 5.27 (1H, m), 5.12-5.03 (1H, m), 4.55 (2H, m), 4.25 (1H, m), 3.64-3.43 (1H, m), 3.24-3.12 (1H, m), 2.80-1.67 (9H, m). Anal. Calcd for C₂₅H₂₆N₄O₇·2H₂O: C, 56.60; H, 5.70; N, 10.56. Found: C, 56.70; H, 5.80; N, 10.33. MS (ES⁺, m/z), 493 (M⁺ - 1, 100%).
- 10 **[3S(1S,9S)] 3-[6,10-Dioxo-4-(hydroxy-3,5-dimethylbenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (214w)**, was prepared by a similar method as compound 214e to afford 210mg (62%) of a
- 15 white solid: mp. >260°C; $[\alpha]_D^{20}$ -93° (c 0.20, MeOH); IR (KBr) 3401, 2948, 1651, 1604, 1559, 1486, 1421, 1325, 1276, 1210; ¹H NMR (D₆-DMSO) δ 9.39 (1H, bs), 8.29 (1H, d, J = 5.9), 7.55 (2H, s), 6.64 (1H, d, J = 6.1), 5.79 (1H, s), 5.25-5.21 (1H, m), 1.90-1.82 (1H, m), 4.41-
- 20 3.69 (2H, m), 3.47-3.20 (3H, m), 2.97-2.91 (1H, m), 2.23 (6H, s), 2.25-1.60 (7H, m).



550q R= Et

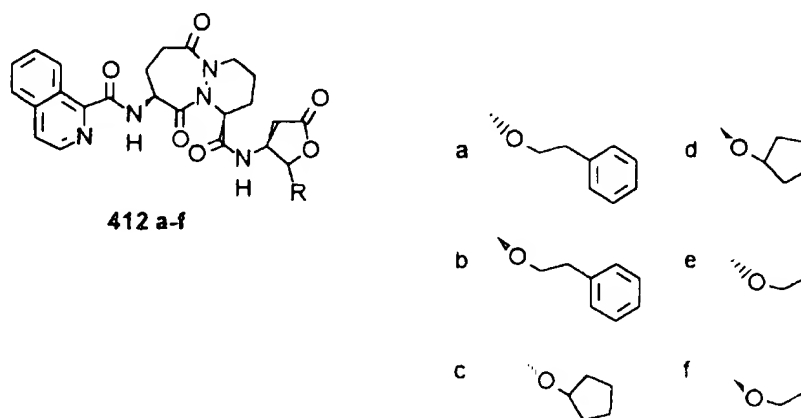
213y R= Bn

[1S,9S(2RS,3S)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-

- 580 -

octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550q), was synthesized via methods used to prepare 213e to afford 550q.

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213y), was synthesized via methods used to prepare 213e to afford 213y.



[1*S*,9*S*(2*S*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412a) was synthesized via methods used to prepare 550q using 513a-1 to afford 412a.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412b) was synthesized via

- 581 -

methods used to prepare 550q using 513a-2 to afford 412b.

[1*S*, 9*S*(2*S*, 3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-

- 5 1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412c) was synthesized via methods used to prepare 550q using 513b-1 to afford 412c.

[1*S*, 9*S*(2*R*, 3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-

- 10 1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412d) was synthesized via methods used to prepare 550q using 513b-2 to afford 412d: ¹H NMR (CDCl₃) δ 9.5 (1H, d),
15 8.9 (1H, d), 8.5 (1H, d), 7.9-7.8 (2H, m), 7.8-7.65 (2H, m), 6.55 (1H, d), 5.55 (1H, d), 5.25-5.1 (2H, m), 4.75-4.65 (1H, m), 4.65-4.6 (1H, m), 4.4-4.3 (1H, m), 3.25-3.15 (1H, m), 3.15-3.05 (1H, m), 2.95-2.8 (2H, m), 2.55-2.4 (2H, m), 2.15-1.5 (14H, m).

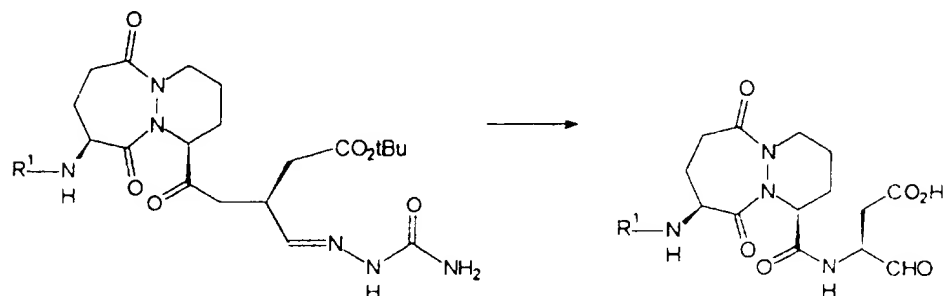
- 20 [1*S*, 9*S*(2*S*, 3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (412e) was synthesized via methods used to prepare 550q using 513f-1 to afford 412e.

- 25 [1*S*, 9*S*(2*R*, 3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-

- 582 -

carboxamide, (412f) was synthesized via methods used to prepare 550q using 513f-2 to afford 412f.

Compounds 410 and 412 were prepared via methods used to prepare 605 from 604.



5

502y, 502z

410, 412

compound	R ¹
502y, 410	
502z, 412	

[3S(1S,9S)] 3-[(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-
 10 6H-pyridazino[1,2-a][1,2]diazepine-9-(thiophene-3-yl-
 carbonylamino)-1-carboxamido]-4-oxobutanoic acid (410),
 was purified by flash chromatography (5-25% methanol in
 dichloromethane) to give 296mg (94%) of a colourless
 solid: mp. 90-200°C; IR (KBr) 3338, 3096, 2950, 1787,
 15 1726, 1657, 1546, 1420, 1279, 1258, 1125, 1092, 984,

- 583 -

933; ¹H NMR (CD₃OD) δ 8.41 (1H, d), 8.13 (1H, d), 7.54-7.41 (3H, m), 7.20 (1H, d), 5.19-5.11 (1H, m), 4.54-4.30 (1H, m), 3.27 (1H, m), 3.18-3.03 (1H, m), 2.81-2.64 (2H, m), 2.56-1.59 (7H, m). Anal. Calcd for C₁₉H₂₂N₄O₇S·2.5H₂O: C, 46.05; H, 5.49; N, 11.31. Found: C, 46.36; H, 5.25; N, 11.10. MS (ES⁺) 449 (M - 1, 80%), 113 (100). Accurate mass calculated for C₁₉H₂₃N₄O₇S (MH⁺): 451.1287. Found: 451.1295.

[3S(1S,9S)] 3-[6,10-Dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (412) was prepared by a similar method to that described for compound 605 to afford a white glassy solid (69%): mp. 138-141°C; [α]_D²³ -105.5° (c 0.5, CH₂Cl₂); IR (KBr) 3375, 1787, 1659, 1515, 1421, 1278, 1256; ¹H NMR (CDCl₃) δ 9.32 (1H, m), 8.79 (1H, m), 8.47 (1H, m), 7.86-7.64 (4H, m), 5.31, 5.18, 4.59, 4.37 (4 or 5H, m), 3.55-2.76, 2.49-2.39, 2.05, 1.65 (11H, 4m). Anal. Calcd for C₂₄H₂₅N₅O₇·1.5H₂O: C, 55.17; H, 5.40; N, 13.40. Found: C, 54.87; H, 5.22; N, 13.15. MS (ES⁺, m/z) 494 (M⁺ - 1, 100%).

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-carbonylamino)-1-carboxamido]-4-oxobutanoate semicarbazone (502y), was synthesized via methods used to prepare 604 from 603 to afford a pale cream powder: mp. 120-180°C; [α]_D²³ -109° (c 0.18, CH₂Cl₂); IR (KBr) 3478, 3327, 1670, 1582, 1543, 1421, 1279, 1257, 1155; ¹H NMR (CDCl₃, CD₃OD) δ 8.04 (1H, m), 7.49 (1H, m), 7.38 (1H, m), 7.17 (1H, m),

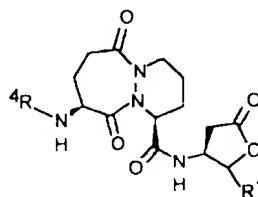
- 584 -

5.17-5.01 (2H, m), 4.86 (1H, m), 4.61-4.50 (1H, m),
 3.45-3.29 (2H, m), 3.21-3.03 (1H, m), 2.79-2.54 (3H,
 m), 2.43-2.33 (1H, m), 2.11-1.66 (5H, m), 1.44 (9H, s).

Anal. Calcd for $C_{24}H_{33}N_7O_7S \cdot H_2O$: C, 49.56; H, 6.07; N,
 5 16.86; S, 5.51. Found: C, 49.51; H, 5.93; N, 16.31; S,
 5.17. MS (ES^+) 586 (100%), 564 ($M^+ + 1$, 1.59).

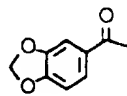

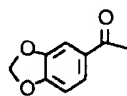
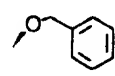
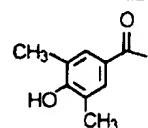
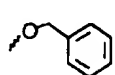
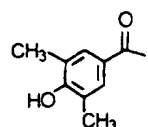
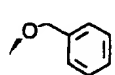
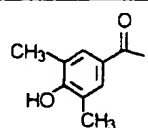
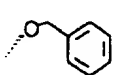
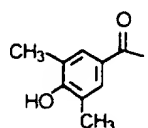
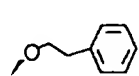
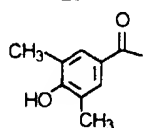
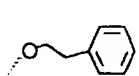
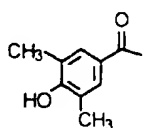
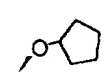
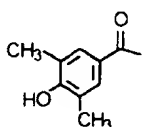
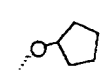
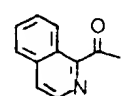
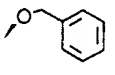
Accurate mass calculated for $C_{24}H_{34}N_7O_7S$ (MH^+):
 564.2240. Found: 564.2267.

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(isoquinolin-1-
 10 oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-
 pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-
 oxobutanoate semicarbazone (502z), was prepared by a
 similar method to that described for compound 604 to
 afford a pale yellow solid (90%): mp. 142-145°C; $[\alpha]_D^{24}$
 15 -136.5° (c 0.06, CH_2Cl_2); 1H NMR ($CDCl_3$) δ 9.51-9.46 (1H,
 m), 9.11 (1H, s), 8.83 (1H, d, J = 7.8), 8.53 (1H, d, J
 = 5.5), 7.89-7.83 (2H, m), 7.77-7.65 (2H, m), 7.55 (1H,
 d, J = 7.2), 7.18 (1H, d, J = 2.7), 5.26-5.12 (2H, m),
 4.87 (1H, m), 4.59 (1H, m), 3.25-3.12 (2H, m), 2.95-
 20 2.76 (2H, m), 2.59-2.38, 2.18-1.94, 1.70 (5H, 3m), 1.44
 (9H, s).



compound	R^4	R^1
415a		

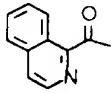
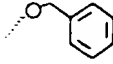
- 585 -

compound	R ⁴	R ¹
415b		
415c		
214w-1		
214w-2		
214w-3		
214w-4		
214w-5		
214w-6		
214w-7		
412g		

5

10

- 586 -

compound	R ⁴	R ¹
412h		

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]

5 diazepine-1-carboxamide, (415a) was synthesized via methods used to prepare 550q to afford 415a.

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]

10 diazepine-1-carboxamide, (415b) was synthesized via methods used to prepare 550q to afford 415b.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]

15 diazepine-1-carboxamide, (415c) was synthesized via methods used to prepare 550q to afford 415c.

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-

20 pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-1) was synthesized via methods used to prepare 550q to afford 214w-1.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-

- 587 -

1,2,3,4,7,8,9,10-octahydro-6-H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-2)
was synthesized via methods used to prepare 550q to
afford 214w-2.

- 5 [1*S*,9*S*(2*S*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-
yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-
1,2,3,4,7,8,9,10-octahydro-6-H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-3)
was synthesized via methods used to prepare 550q to
10 afford 214w-3.

- [1*S*,9*S*(2*R*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-
yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-
1,2,3,4,7,8,9,10-octahydro-6-H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-4)
15 was synthesized via methods used to prepare 550q to
afford 214w-4.

- [1*S*,9*S*(2*S*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-
yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-
1,2,3,4,7,8,9,10-octahydro-6-H-
20 pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-5)
was synthesized via methods used to prepare 550q to
afford 214w-5.

- [1*S*,9*S*(2*R*,3*S*)] N-(2-Cyclopentoxo-5-oxotetrahydrofuran-
3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-
25 hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-6)
was synthesized via methods used to prepare 550q to
afford 214w-6.

- 588 -

[1*S*,9*S*(2*S*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide, (214w-7)

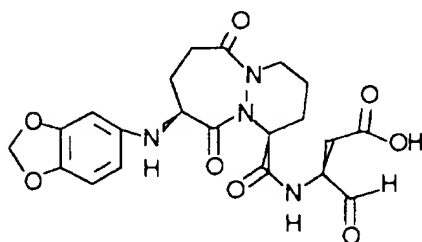
5 was synthesized via methods used to prepare 550q to afford 214w-7.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-

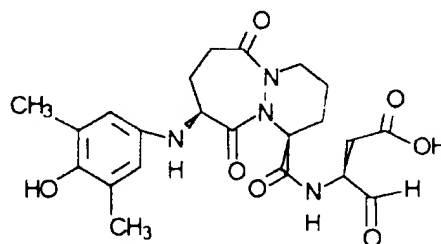
1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-*a*][1,2]
10 diazepine-1-carboxamide, (412g) was synthesized via
methods used to prepare 550q to afford 412g.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-

1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-*a*][1,2]
15 diazepine-1-carboxamide, (412h) was synthesized via
methods used to prepare 550q to afford 412h.



415



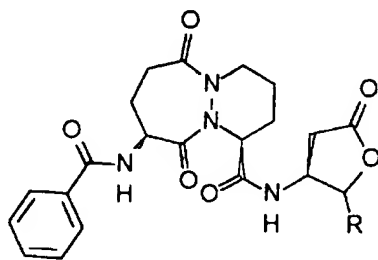
214w

[3*S*(1*S*,9*S*)] 3-(9-(4,5-Methylenedioxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-

20 oxobutanoic acid (415), was synthesized by the method
used to prepare 2002 from 2001 to afford 415.

- 589 -

[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214*w*), was synthesized by the method used to prepare 2002 from 2001 to afford 214*w*.

2100*k-o*

compound	R
2100 <i>k</i>	
2100 <i>l</i>	
2100 <i>m</i>	
2100 <i>n</i>	
2100 <i>o</i>	

- 590 -

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-phenethyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100k),

5 was prepared by a similar method as compound 213e to afford a mixture of diastereoisomers (75/25) as a white solid (258mg, 83%): mp. 101°C; $[\alpha]_D^{25}$ -96° (c 0.2, CH₂Cl₂); IR (KBr) 3328, 2935, 2978, 1732, 1669, 1603, 1483, 1450, 1414, 1237, 1155, 1082, 989, 755; ¹H NMR
10 (CDCl₃) δ 7.84-7.80 (2H, m), 7.54-7.17 (8H, m), 7.06-6.99 (1H, m), 6.25 (1H, d, J = 7.9H), 5.41 (0.75H, d, J = 5.4H), 5.31 (0.25H, bs), 5.23-5.09 (1H, m), 4.93-4.87 (1H, m), 4.68-4.51 (2H, m), 4.40-4.33 (0.25H, m), 4.24-4.14 (0.75H, m), 3.95-3.70 (1H, m), 3.30-3.13 (1H, m),
15 3.14-2.78 (5H, m), 2.47-2.21 (2H, m), 2.05-1.50 (5H, m). Anal. Calcd for C₂₉H₃₂N₄O₇•0.5H₂O: C, 62.47; H, 5.97; N, 10.05. Found: C, 62.17; H, 5.83; N, 9.97. MS (ES⁺) 549.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzamido-N-(2-cyclopentyloxy-5-oxo-
20 tetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100l), was prepared by a similar method as 213e, (74%) as a colourless solid: mp. 172-80°C; $[\alpha]_D^{23}$ -91.5° (c 0.1, CH₂Cl₂); IR (KBr) 3290, 1792,
25 1677, 1657, 1642, 1544, 1425, 1280, 1259, 1124, 977; ¹H NMR (CDCl₃) δ 7.80 (2H, m), 7.46 (3.5H, m), 7.00 (1H, d, J = 6.7), 6.48 (0.5H, d, J = 7.9), 5.55 (0.5H, d, J = 5.3), 5.19 (2H, s + m), 4.93 (0.5H, m), 4.62 (1.5H, m), 4.34 (1H, m), 4.18 (0.5H, m), 3.28-2.70 (4H, m), 2.49-
30 2.29 (2H, m), 2.05-1.48 (15H, m).

- 591 -

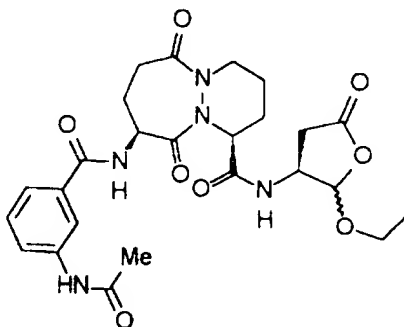
[1S,9S(2R,3S)] 9-Benzamido-6,10-dioxo-N-[2-(2-indanyloxy)-5-oxo-tetrahydrofuran-3-yl]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100m),

5 was prepared by a similar method as 213e, (76%) as a colourless solid: mp. ~140°C, remelts 187-9°C; $[\alpha]_D^{23}$ -96.9° (c 0.11, CH₂Cl₂); IR (KBr) 3507, 3308, 3251, 1772, 1660, 1641, 1566, 1545, 1457, 1424, 1346, 1326, 1302, 1275, 1258, 1136, 1085, 1018, 981; ¹H NMR (CDCl₃)
10 δ 7.78 (2H, m), 7.53 (3H, m), 7.19 (4H, m), 6.91 (1H, d, J = 7.4), 6.27 (1H, d, J = 7.6), 5.66 (1H, d, J = 5.3), 5.10 (1H, m), 4.96 (1H, m), 4.75 (2H, m), 4.52 (1H, m), 3.08 (3H, m), 3.03-2.71 (5H, m), 2.48-2.31 (2H, m), 1.90-1.40 (4H, m), 1.22 (1H, m).

15 [1S,9S(2S,3S)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100n), was prepared by a similar method to that described for compound 213e to afford a white
20 glassy solid (76%): mp. 112-5°C; $[\alpha]_D^{23}$ -62.0° (c 0.1, CH₂Cl₂); IR (KBr) 3305, 1789, 1677, 1665, 1535, 1422, 1279, 1256, 1119, 942, 700; ¹H NMR (CDCl₃) δ 7.84 (2H, m), 7.58-7.27 (9H, m), 6.99 (1H, d, J = 7.8), 5.23 (1H, s), 5.23-5.11 (1H, m), 4.89 (1H, m), 4.76 (1H, d, J =
25 11.3), 4.55 (1H, d, J = 11.4), 4.58-4.43 (2H, m), 3.30-2.96, 2.81-2.69, 2.46-2.37, 2.16-1.66 (10H, 4m), 2.27 (1H, d, J = 17.8). Anal. Calcd for C₂₈H₃₀N₄O₇•0.5H₂O: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.88; H, 5.70; N, 10.33. MS (ES⁺, m/z) 535 (M⁺ + 1, 100%).

- 592 -

[1*S*,9*S*(2*R*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100o), (containing about 7% of (2*S*)), was prepared by a similar method to that described for compound 213e to afford a white glassy solid (81%): mp. 115-7°C; $[\alpha]_D^{23}$ -121.8° (c 0.11, CH₂Cl₂); IR (KBr) 3326, 1792, 1659, 1535, 1421, 1278, 1257, 1124, 978; ¹H NMR (CDCl₃) δ 7.82 (2H, m), 7.58-7.24 (8H, m), 6.90 (1H, d, J = 7.3), 6.49 (1H, d, J = 7.7), 5.57 (1H, d, J = 5.5), 5.11 (2H, m), 4.91 (1H, d, J = 11.4), 4.57 (1H, d, J = 11.1), 4.81-4.68 (1H, m), 4.65-4.54 (1H, m), 3.18-2.71 2.52-2.30, 2.05-1.62 (11H, 3m). Anal. Calcd for C₂₈H₃₀N₄O₇•0.5H₂O: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.70; H, 5.71; N, 10.15. MS (ES⁺, m/z) 535 (M⁺ + 1, 94.3%), 557 (100%).



550n

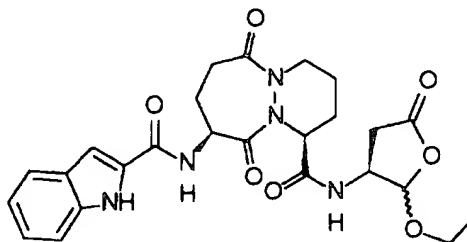
[1*S*,9*S*(2*R*,3*S*)] 9-(3-Acetamido)benzoylamino-6,10-dioxo-N-(2-ethoxy-5-oxo-tetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550n), was prepared by a similar method as compound 213e to

- 593 -

afford a mixture of diastereoisomers (65/35) as a tan powder (390mg, 28%): mp. 139-145°C; $[\alpha]_D^{23}$ -104° (c 0.2, MeOH); IR (KBr) 3318, 2405, 2369, 1792, 1660, 1591, 1549, 1484, 1422, 1257, 1117; ^1H NMR (D_6 -DMSO) δ

5 10.1 (1H, s), 8.80 (0.65H, d, $J = 6.6$), 8.58 (0.35H, d, $J = 6.6$), 8.59 (1H, d, $J = 7.0$), 8.06 (1H, bs), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 7.47-7.39 (1H, m), 5.61 (0.35H, d, $J = 5.0$), 5.37 (0.65H, bs), 5.17-5.14 (0.35H, m), 5.08-5.06 (0.65H, m), 4.92-4.86 (1H, m),

10 4.67-4.61 (0.35H, m), 4.47-4.41 (0.65H, m), 4.28-4.11 (1H, 2m), 3.80-3.59 (2H, m), 3.23-2.75 (3H, m), 2.61-1.48 (7H, m), 2.10 (3H, s), 1.25 and 1.17 (3H, 2t, $J = 5.8$). MS (ES^+) 528.



550o

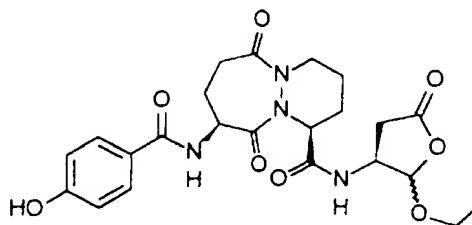
15 [1*S*,9*S*(2*RS*,3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(2-indoloylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550o),

was synthesized by a similar method as compound 213e to

20 afford a colourless solid (1.071g, 80%): mp. 155-70°C; $[\alpha]_D^{22}$ -75.8° (c 0.26, CH_2Cl_2); IR (KBr) 3314, 2941, 1791, 1658, 1545, 1420, 1341, 1312, 1252, 1181, 1118, 939, 749; ^1H NMR (CDCl_3) δ 9.45 (0.5H, s), 9.34 (0.5H, s), 7.68-7.62 (1H, m), 7.49-7.39 (2H, m), 7.33-7.26

- 594 -

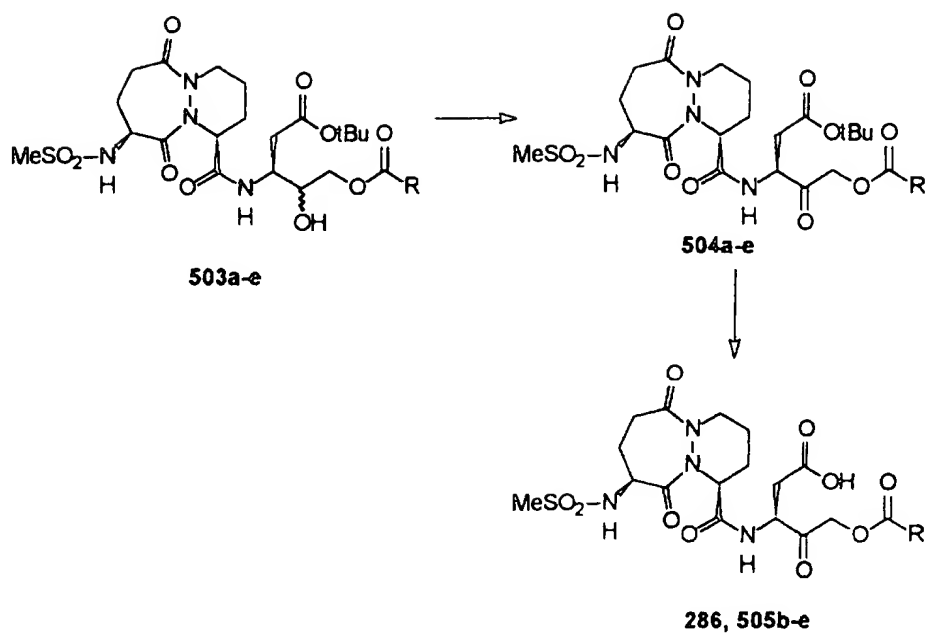
(1H, m), 7.18-7.03 (3H, m), 5.49 (0.5H, d), 5.30 (0.5H, s), 5.26-5.13 (1H, m), 4.90-4.83 (0.5H, m), 4.76-4.49 (1H, m), 4.42-4.35 (0.5H, m), 3.97-3.74 (1H, m), 3.72-3.53 (1H, m), 3.35-2.64 (4H, m), 2.50-2.37 (1H, m), 2.20-1.82 (5H, m), 1.69-1.50 (2H, m), 1.30-1.19 (3H, m).

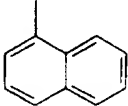
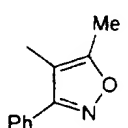
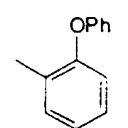
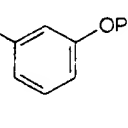


550p

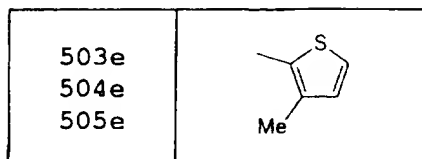
[1*S*,9*S*(2*RS*,3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(4-hydroxybenzoyl)amino-
 10 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (550p),
 was prepared by a similar method as compound 213e to afford a mixture of diastereoisomers as a white foam (820mg, 47%): $[\alpha]_D^{24}$ -75° (c 0.16, CH₂Cl₂); IR (KBr) 3401, 2937, 1791, 1657, 1609, 1539, 1505, 1423, 1277, 1177, 1118; ¹H NMR (CDCl₃) δ 8.07-8.05 (1H, m), 7.67 (2H, d, J = 7.9), 7.38-7.29 (2H, m), 6.80 (2H, d, J = 8.5), 5.49 (0.5H, d, J = 4.6), 5.23 (0.5H, bs), 5.24-5.20 (1H, m), 5.12-5.08 (1H, m), 4.68-4.29 (2H, m), 3.92-3.45 (3H, m), 3.32-2.30 (2H, m), 2.80-1.56 (11H, m), 1.21 (3H, t, J = 7.0H).

- 595 -



compound	R
503a 504a 286	
503b 504b 505b	
503c 504c 505c	
503d 504d 505d	

- 596 -



[3*S*,4*R*(1*S*,9*S*)] *t*-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-hydroxy-5-(1-naphthoyloxy)pentanoate (503a), was prepared from 212b and (3*S*,4*R*) *t*-butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoyloxy)pentanoate by the method described for (213e) to afford 533mg (81%) of an off-white foam: $[\alpha]_D^{22} -81.4^\circ$ (c 0.5, CH₂Cl₂); IR(KBr) 3342, 2976, 1719, 1664, 1328, 1278, 1246, 1153, 1137. ¹H NMR (CDCl₃) δ 8.86 (1H, d, *J* = 8.4), 8.21 (1H, dd, *J* = 1.3, 7.3), 8.03 (1H, d, *J* = 8.1), 7.88 (1H, d, *J* = 8.6), 7.66-7.45 (3H, m), 7.23 (1H, d, *J* = 8.6), 5.96 (1H, d, *J* = 9.2), 5.30 (1H, m), 4.59-4.33 (5H, m), 4.24 (1H, m), 3.96 (1H, brd), 3.29 (1H, m), 2.95 (1H, m), 2.93 (3H, s), 2.69-2.50 (3H, m), 2.36 (1H, m), 1.96 (4H, m), 1.62 (1H, m), 1.41 (9H, s). Anal. Calcd for C₃₁H₄₀N₄O₁₀S•0.25H₂O : C, 55.97; H, 6.14; N, 8.42. Found: C, 55.90; H, 6.11; N, 8.23. M.S. (ES⁺) 683 (M+Na, 100%), 661 (M+1,39), 605 (78).

[3*S*(1*S*,9*S*)] *t*-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(1-naphthoyloxy)-4-oxopentanoate (504a), was synthesized from 503a via method used to prepare 216e from 215e to afford 446mg (91%) of a colourless foam: $[\alpha]_D^{21} -111.6^\circ$

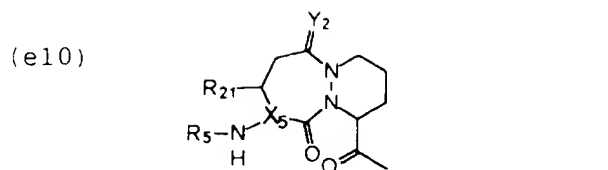
- 597 -

(c 0.5, CH₂Cl₂); IR (KBr) 3319, 2978, 2936, 1723, 1670, 1413, 1370, 1329, 1278, 1246, 1153. ¹H NMR (CDCl₃) δ 8.87 (1H, d, J = 8.9), 8.29 (1H, d, J = 7.2), 8.06 (1H, d, J = 8.3), 7.90 (1H, d, J = 8.2), 7.66-7.48 (3H, m), 7.37 (1H, d, J = 8.1), 5.61 (1H, d, J = 9.0), 5.31 (1H, m), 5.22 (1H, AB, J = 16.9), 5.09 (1H, AB, J = 16.92), 4.99 (1H, m), 4.65-4.43 (2H, m), 3.28 (1H, m), 2.96 (3H, s), 2.86 (2H, m), 2.59 (1H, m) 2.38 (1H, dd, J = 6.8, 13.2), 2.21-1.70 (6H, m), 1.45 (9H, s). Anal. Calcd for C₃₁H₃₈N₄O₁₀S•0.25H₂O. C, 56.14; H, 5.85; N, 8.45. Found: C, 56.11; H, 5.83; N, 8.29. M.S. (ES⁺) 657 (M-1, 100%).

[3S(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(1-naphthoyloxy)-4-oxopentanoic acid (286), was prepared from 504a by the method described for 217 to afford 356mg (93%) of a white powder: mp 120-123°C; [α]_D²³ -121° (c 0.194, CH₂Cl₂); IR (KBr) 3314, 2937, 1722, 1663, 1412, 1328, 1278, 1245, 1195, 1132. ¹H NMR (d6-DMSO) δ 12.63 (1H, brs), 8.94 (1H, d, J = 7.4), 8.78 (1H, d, J = 8.6), 8.26 (2H, m), 8.11 (1H, d, J = 8.0), 7.77-7.62 (4H, m), 5.28 (2H, s), 5.21 (1H, m), 4.82 (1H, m), 4.44-4.29 (2H, m), 3.31 (1H, m), 2.98 (3H, s), 2.98-2.86 (2H, m), 2.72 (1H, dd, J = 7.3, 16.9), 2.40 (1H, m), 2.24-1.84 (4H, m), 1.69 (2H, m). Anal. Calcd for C₂₇H₃₀N₄O₁₀S•H₂O : C, 52.25; H, 5.20; N, 9.03. Found: C, 52.11; H, 4.97; N, 8.89. M.S. (ES⁺) 601 (M-1, 100%).

[3S,4RS(1S,9S)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-9-

- 797 -



R_3 is $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$ and R_{11} is $-\text{Ar}_4$;

R_5 is selected from the group consisting of:

- 5 $-\text{C}(\text{O})-\text{R}_{10}$,
 $-\text{C}(\text{O})\text{O}-\text{R}_9$, and
 $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$;

X_5 is CH ;

Y_2 is O ;

10 T_1 is O or S ;

each R_9 is independently selected from the group consisting of $-\text{Ar}_3$ and a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, wherein
 15 the $-\text{C}_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of $-\text{H}$, $-\text{Ar}_3$, a $-\text{C}_{3-6}$ cycloalkyl group, and a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, wherein the $-\text{C}_{1-6}$ alkyl group is
 20 optionally unsaturated;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, $-\text{OH}$, $-\text{OR}_9$, $-\text{CO}_2\text{H}$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl,

- 796 -

pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

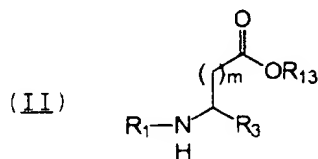
each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and



wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

35. A compound represented by the formula:

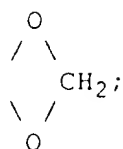


wherein:

m is 1;

25 R_1 is:

- 795 -



5

provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

10

34. The compound according to claims 32 or 33, wherein:

m is 1;

15 R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, $-\text{OH}$, $-\text{OR}_9$, $-\text{CO}_2\text{H}$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

20 R_{21} is $-\text{H}$ or $-\text{CH}_3$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, 25 isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-\text{Q}_1$;

30 each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,

- 794 -

-C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

5 R₁₃ is selected from the group consisting of H, Ar₃, and a C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

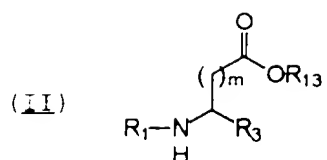
OR₁₃ is optionally -N(H)-OH;

10 each R₂₁ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

15 each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally
20 containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

25 each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, -OR₉, -NHR₉, -R₉, -C(O)-R₁₀, and

- 793 -



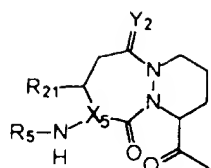
wherein:

m is 1 or 2;

R₁ is:

5

(e10)



;

R₃ is -C(O)-H;R₅ is selected from the group consisting of:

- 10
- S(O)₂-R₉,
 - S(O)₂-NH-R₁₀,
 - C(O)-C(O)-R₁₀,
 - R₉, and
 - C(O)-C(O)-OR₁₀;

15

X₅ is CH;Y₂ is H₂ or O;

each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

20

each R₁₀ is independently selected from the group consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a

- 792 -

and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains
 5 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, $-NH-$,
 10 $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

15 each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, R_5 , $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and



25 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

33. A compound represented by the formula:

- 791 -

Y_2 is H_2 or O;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein
5 the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of $-H$, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is
10 optionally unsaturated;

R_{13} is selected from the group consisting of H , Ar_3 , and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

15 OR_{13} is optionally $-N(H)-OH$;

each R_{21} is independently selected from the group consisting of $-H$ or a $-C_{1-6}$ straight or branched alkyl group;

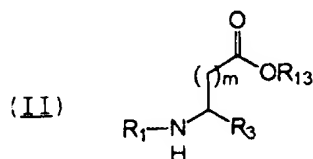
each Ar_3 is a cyclic group independently selected
20 from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom
25 group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,

- 790 -

with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

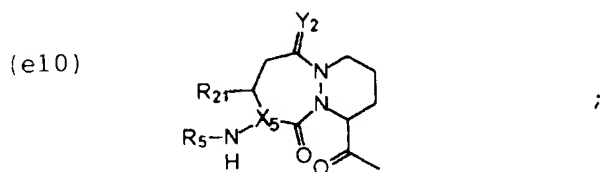
32. A compound represented by the formula:



wherein:

```
10      m is 1 or 2;
```

R_1 is:



15 R_3 is $-C(O)-CH_2-T_1-R_{11}$; T_1 is O; and R_{11} is $-C(O)-Ar_4$;

R_5 is selected from the group consisting of:

$$-S(O)_2-R_9,$$
$$-S(O)_2-NH-R_{10},$$
$$-C(O)-C(O)-R_{10},$$

20 $-R_9$, and

$$-C(O)-C(O)-OR_{10};$$

X_5 is CH;

- 789 -

wherein the phenyl is optionally substituted with Q_1 ;

R_{21} is -H or -CH₃;

Ar_2 is (hh);

Y is O;

5

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by - Q_1 ;

10

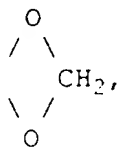
each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by - Q_1 ;

15

each Q_1 is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and

20

25



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted

- 788 -



wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

10 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

30. The compound according to claims 26 or 27, wherein R_5 is selected from the group consisting of:

15

- $-S(O)_2-R_9$,
- $-S(O)_2-NH-R_{10}$,
- $-C(O)-C(O)-R_{10}$,
- 20 $-R_9$, and
- $-C(O)-C(O)-OR_{10}$.

31. The compound according to claim 30, wherein:

m is 1;

25

T_1 is O or S;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl,

30

- 787 -

T_1 is O or S;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain
5 alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

R_{21} is $-H$ or $-CH_3$;

Ar_2 is (hh);

Y is O;

10

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl,
15 thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected
20 from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group
25 consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

- 786 -

heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, -R₅, -OR₅, -NHR₅, -OR₉, -NHR₉, -R₉, -C(O)-R₁₀, and



provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

28. The compound according to claims 26 or 27, wherein R₅ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

29. The compound according to claim 28, wherein:

m is 1;

- 785 -

consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

- 5 R₁₃ is selected from the group consisting of H, Ar₃, and a C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

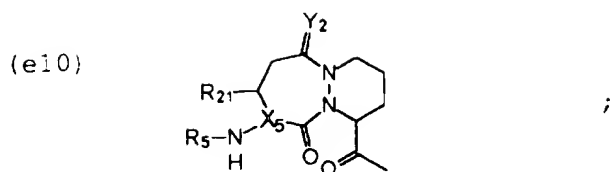
OR₁₃ is optionally -N(H)-OH;

- 10 each R₂₁ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

- each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains
15 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
20 -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

- 25 each Ar₄ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said

- 784 -



R_3 is $-C(O)-CH_2-T_1-R_{11}$ and R_{11} is $-(CH_2)_{1-3}-Ar_4$;

R_5 is selected from the group consisting of:

- 5 $-C(O)-R_{10}$,
 $-C(O)O-R_9$,
 R_{10}
 /
 $-C(O)-N$
 \
 R_{10} ,
 10 $-S(O)_2-R_9$,
 $-C(O)-CH_2-O-R_9$,
 $-C(O)C(O)-R_{10}$,
 15 $-R_9$,
 $-H$, and
 $-C(O)C(O)-OR_{10}$,

X_5 is CH ;

Y_2 is H_2 or O ;

20 each T_1 is independently selected from the group
 consisting of $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

 each R_9 is independently selected from the group
 consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched
 25 alkyl group optionally substituted with $-Ar_3$, wherein
 the $-C_{1-6}$ alkyl group is optionally unsaturated;

 each R_{10} is independently selected from the group

- 783 -

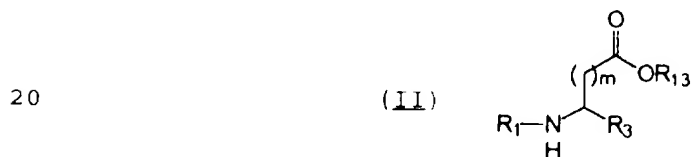
containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

5 each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, R_5 , $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and



15 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

27. A compound represented by the formula:



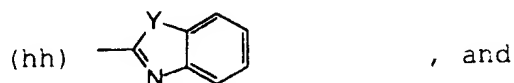
wherein:

m is 1 or 2;

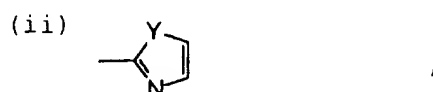
R_1 is:

- 782 -

group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1 :



5



wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, $-NH-$, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally

- 781 -

-S(O)₂-R₉,
-C(O)-CH₂-O-R₉,
-C(O)C(O)-R₁₀,
-R₉,
5 -H, and
 -C(O)C(O)-OR₁₀,

X₅ is CH;

Y₂ is H₂ or O;

each R₉ is independently selected from the group
10 consisting of -Ar₃ and a -C₁₋₆ straight or branched
 alkyl group optionally substituted with -Ar₃, wherein
 the -C₁₋₆ alkyl group is optionally unsaturated;

each R₁₀ is independently selected from the group
consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a
15 -C₁₋₆ straight or branched alkyl group optionally
 substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is
 optionally unsaturated;

R₁₃ is selected from the group consisting of H,
Ar₃, and a C₁₋₆ straight or branched alkyl group
20 optionally substituted with -Ar₃, -CONH₂, -OR₅, -OH,
 -OR₉, or -CO₂H;

OR₁₃ is optionally -N(H)-OH;

each R₂₁ is independently selected from the group
consisting of -H or a -C₁₋₆ straight or branched alkyl
25 group;

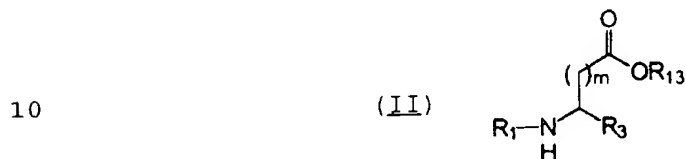
Ar₂ is independently selected from the following

- 780 -

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

5 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

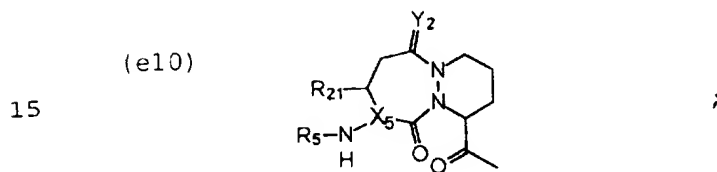
26. A compound represented by the formula:



wherein:

m is 1 or 2;

R_1 is:



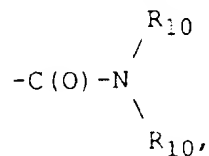
R_3 is $-CO-Ar_2$;

R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

20



- 779 -

wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

R_{21} is -H or -CH₃;

5 Ar_2 is (hh);

Y is O;

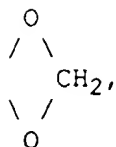
each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by - Q_1 ;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by - Q_1 ;

each Q_1 is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, - R_9 , -NH- R_5 wherein R_5 is -C(O)- R_{10} or -S(O)₂- R_9 , -OR₅ wherein R_5 is -C(O)- R_{10} , -OR₉, -NHR₉, and



- 778 -



5

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

10 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

24. The compound according to any one of
15 claims 19-21, wherein R_5 is selected from the group consisting of:

20 $-S(O)_2-R_9$,
 $-S(O)_2-NH-R_{10}$,
 $-C(O)-C(O)-R_{10}$,
 $-R_9$, and
 $-C(O)-C(O)-OR_{10}$.

25. The compound according to claim 24,
 wherein:

25 m is 1;

T_1 is O or S,

provided that when R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1
 is O;

30 R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$,

- 777 -

provided that when R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$,
5 wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

R_{21} is $-H$ or $-CH_3$;

Ar_2 is (hh);

10 Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,
15 isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

20 each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

25 each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

- 776 -

16. The compound according to claim 8,
wherein R_1 is (e10) and X_5 is N.

17. The compound according to claim 16,
wherein R_3 is CO-Ar₂.

5 18. The compound according to claim 16,
wherein R_3 is -C(O)-CH₂-T₁-R₁₁ and R₁₁ is -(CH₂)₁₋₃-Ar₄.

19. The compound according to claim 16,
wherein:

10 R_3 is -C(O)-CH₂-T₁-R₁₁;
 T_1 is O; and
 R_{11} is -C(O)-Ar₄.

20. The compound according to claim 16,
wherein R_3 is -C(O)-H.

15 21. The compound according to claim 16,
wherein R_3 is -CO-CH₂-T₁-R₁₁ and R₁₁ is -Ar₄.

22. The compound according to any one of
claims 19-21, wherein R_5 is selected from the group
consisting of:

20 -C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

23. The compound according to claim 22,
wherein:

25 m is 1;
 T_1 is O or S,

- 775 -

Y is O;

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

- 774 -

m is 1;

ring C is benzo, pyrido, or thieno;

R₃ is selected from the group consisting of
-C(O)-H, -C(O)-Ar₂, and -C(O)CH₂-T₁-R₁₁;

5 R₅ is selected from the group consisting of:
 -C(O)-R₁₀, wherein R₁₀ is -Ar₃;
 -C(O)O-R₉, wherein R₉ is -CH₂-Ar₃;
 -C(O)C(O)-R₁₀, wherein R₁₀ is -Ar₃;
 -R₉, wherein R₉ is a C₁₋₂ alkyl group
10 substituted with -Ar₃; and
 -C(O)C(O)-OR₁₀, wherein R₁₀ is -CH₂Ar₃;

T₁ is O or S;

R₆ is H;

15 R₈ is selected from the group consisting -C(O)-R₁₀,
 -C(O)-CH₂-OR₁₀, and -C(O)CH₂-N(R₁₀)(R₁₀), wherein R₁₀ is
 H, CH₃, or -CH₂CH₃;

R₁₁ is selected from the group consisting of -Ar₄,
-(CH₂)₁₋₃-Ar₄, and -C(O)-Ar₄;

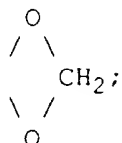
20 R₁₃ is H or a C₁₋₄ straight or branched alkyl group
 optionally substituted with -Ar₃, -OH, -OR₉, -CO₂H,
 wherein the R₉ is a C₁₋₄ branched or straight chain
 alkyl group; wherein Ar₃ is morpholinyl or phenyl,
 wherein the phenyl is optionally substituted with O₁;

25 Ar₂ is (hh);

- 773 -

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, R_5 , $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

5



10

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

15

9. The compound according to claim 8, wherein R_1 is (e11).

10. The compound according to claim 8, wherein R_1 is (e12).

20

11. The compound according to claim 8, wherein R_1 is (y1).

12. The compound according to claim 8, wherein R_1 is (y2).

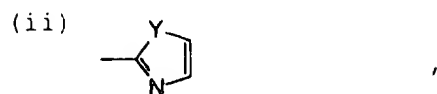
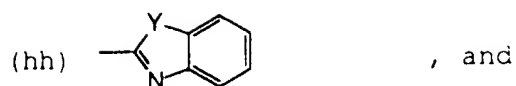
13. The compound according to claim 8, wherein R_1 is (z).

25

14. The compound according to claim 8, wherein R_1 is (w2).

15. The compound according to claim 14, wherein:

- 772 -



wherein each Y is independently selected from the
 5 group consisting of O and S;

each Ar₃ is a cyclic group independently selected
 from the set consisting of an aryl group which contains
 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
 and an aromatic heterocycle group containing between 5
 10 and 15 ring atoms and between 1 and 3 rings, said
 heterocyclic group containing at least one heteroatom
 group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
 -N(R₅)-, and -N(R₉)- said heterocycle group optionally
 containing one or more double bonds, said heterocycle
 15 group optionally comprising one or more aromatic rings,
 and said cyclic group optionally being singly or
 multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected
 from the set consisting of an aryl group which contains
 20 6, 10, 12, or 14 carbon atoms and between 1 and 3
 rings, and a heterocycle group containing between 5 and
 15 ring atoms and between 1 and 3 rings, said
 heterocyclic group containing at least one heteroatom
 group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-,
 25 -N(R₅)-, and -N(R₉)- said heterocycle group optionally
 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic rings,
 and said cyclic group optionally being singly or
 multiply substituted by -Q₁;

- 771 -

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

5 each R_{10} is independently selected from the group consisting of $-H$, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

10 each R_{11} is independently selected from the group consisting of:

$-Ar_4$,
 $-(CH_2)_{1-3}-Ar_4$,
 $-H$, and

15 $-C(O)-Ar_4$;

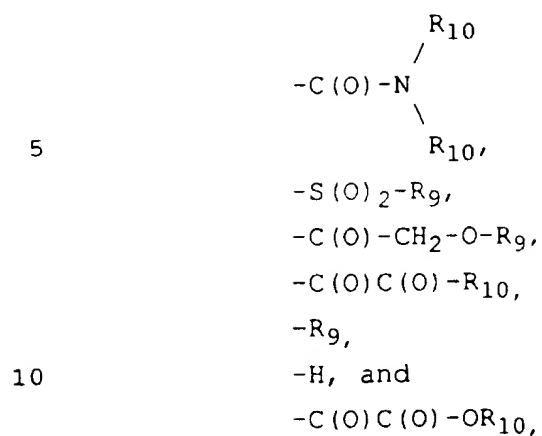
R_{13} is selected from the group consisting of H , Ar_3 , and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

20 OR_{13} is optionally $-N(H)-OH$;

each R_{21} is independently selected from the group consisting of $-H$ or a $-C_{1-6}$ straight or branched alkyl group;

25 Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1 :

- 770 -



Y_2 is H_2 or O ;

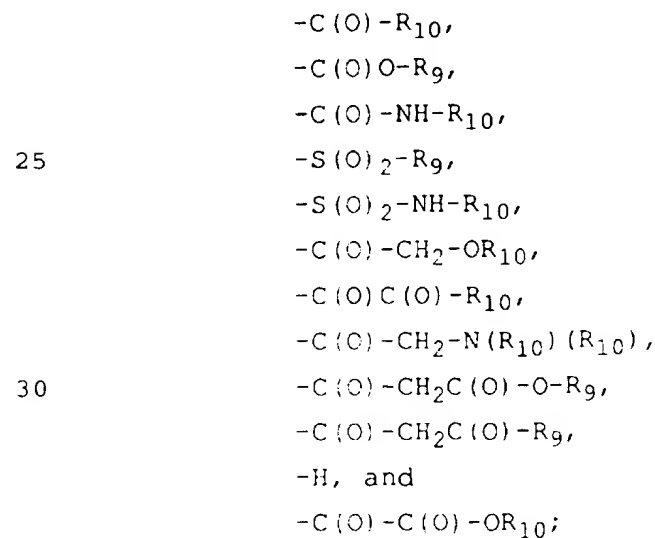
X_7 is $-\text{N}(\text{R}_8)-$ or $-\text{O}-$;

15 each T_1 is independently selected from the group consisting of $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, and $-\text{S}(\text{O})_2-$;

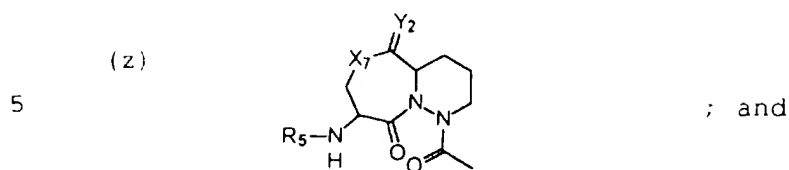
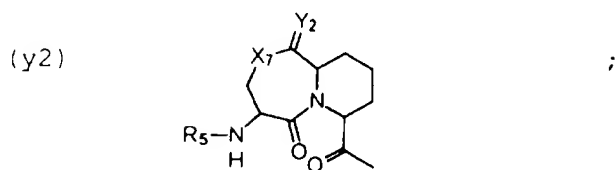
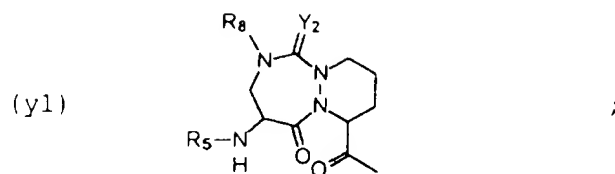
R_6 is selected from the group consisting of $-\text{H}$ and $-\text{CH}_3$;

20

R_8 is selected from the group consisting of:



- 769 -



ring C is chosen from the group consisting of
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,
10 cyclopentyl, and cyclohexyl;

R₃ is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- 15 -C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

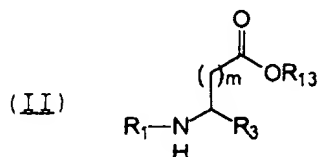
R₅ is selected from the group consisting of:

- C(O)-R₁₀,
- 20 -C(O)O-R₉,

- 768 -

provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

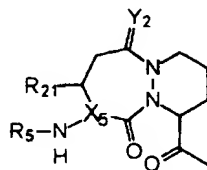
5 8. A compound represented by the formula:



m is 1 or 2;

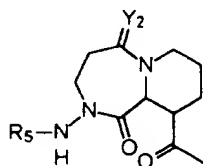
10 R_1 is selected from the group consisting of the following formulae:

(e10)



, wherein X_5 is N;

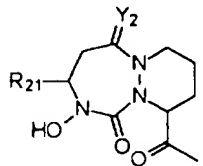
(e11)



15

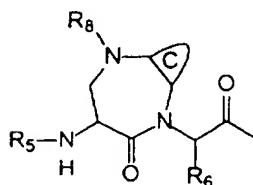
;

(e12)



;

(w2)



;

- 767 -

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl,
 5 wherein the phenyl is optionally substituted with Q_1 ;

R_{21} is $-H$ or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

10 each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,
 15 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$
 20 wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and



wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

30

- 766 -

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, R_5 , $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and



10 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

15 5. The compound according to claim 4, wherein R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,
 $-C(O)O-R_9$, and
 $-C(O)-NH-R_{10}$.

20 6. The compound according to claim 4, wherein R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
 $-S(O)_2-NH-R_{10}$,
 $-C(O)-C(O)-R_{10}$,
25 $-R_9$, and
 $-C(O)-C(O)-OR_{10}$.

7. The compound according to claims 5 or 6, wherein:

m is 1;

30

- 765 -

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3 , and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9 , $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2 , =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

- 764 -

-C(O)C(O)-R₁₀,
 -R₉,
 -H, and
 -C(O)C(O)-OR₁₀;

5 X₅ is -CH- or -N-;
 | |

Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

10

R₆ is selected from the group consisting of -H and
 -CH₃;

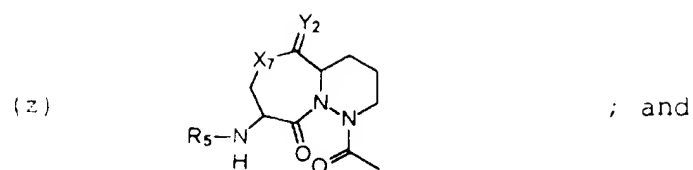
R₈ is selected from the group consisting of:

15

-C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-N(H)-R₁₀,
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 20 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀;
 -C(O)-CH₂N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 -C(O)-CH₂C(O)-R₉,
 25 -H, and
 -C(O)-C(O)-OR₁₀;

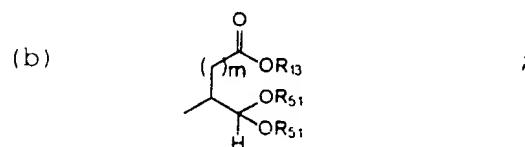
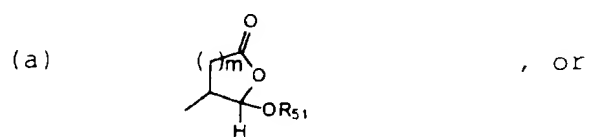
each R₉ is independently selected from the group
 consisting of -Ar₃ and a -C₁₋₆ straight or branched
 alkyl group optionally substituted with -Ar₃, wherein
 30 the -C₁₋₆ alkyl group is optionally unsaturated;

- 763 -



ring C is chosen from the group consisting of
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
5 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,
cyclopentyl, and cyclohexyl;

R₂ is:



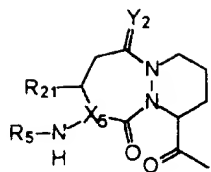
10 m is 1 or 2;

R₅ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
15 $\begin{array}{c} R_{10} \\ / \\ -C(O)-N \\ \backslash \\ R_{10} \end{array}$,
-S(O)₂-R₉,
20 -C(O)-CH₂-O-R₉,

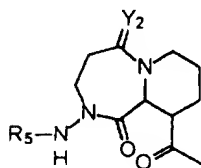
- 762 -

(e10)



;

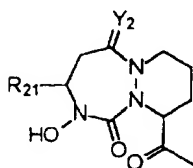
(e11)



;

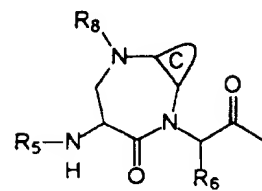
5

(e12)



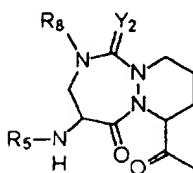
;

(w2)



;

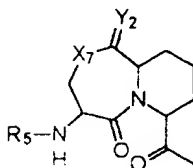
(y1)



;

10

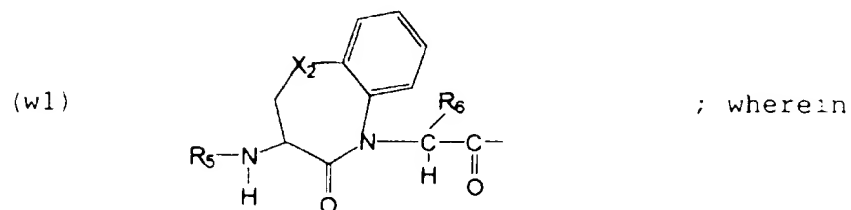
(y2)



;

- 761 -

3. The compound according to claims 1 or 2,
wherein the R_1 group is:



5 X_2 is:

-O- ,
-S- ,
-SO₂-, or
-NH-;

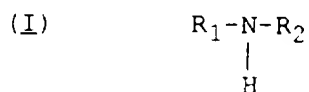
10

optionally substituted with R_5 or Q_1 at X_2 when X_2
is -NH-; and

ring C is benzo substituted with -C₁₋₃ alkyl,
-O-C₁₋₃ alkyl, -Cl, -F or -CF₃.

15

4. A compound represented by the formula:



wherein:

20

R_1 is selected from the group consisting of the
following formulae:

- 760 -

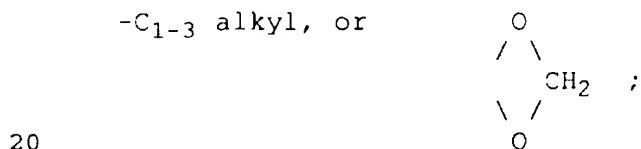
-CO-O-R₉,
 -SO₂-R₉, or
 -CO-NH-R₉,

5 R₇ is -H and R₆ is: -H,
 -R₉, or
 -Ar₁;

R₉ is a C₁₋₆ straight or branched alkyl group optionally substituted with =O and optionally substituted with -Ar₁;

10 R₁₀ is H or a -C₁₋₃ straight or branched alkyl group;

Ar₁ is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl optionally substituted with -O-C₁₋₃ alkyl, -NH-C₁₋₃ alkyl, -N-(C₁₋₃ alkyl)₂, -Cl, -F, -CF₃,
 15 -C₁₋₃ alkyl, or



Q₁ is R₉ or -(CH₂)_{0,1,2}-T₁-(CH₂)_{0,1,2}-Ar₁, wherein T₁ is -O- or -S-;

each X is independently selected from the group consisting of =N-, and =CH-;

25 each X₂ is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-.

- 759 -

X₂ is O,

R₅ is benzyloxycarbonyl, and

ring C is benzo,

then R₃ cannot be -CO-R₁₃ when:

5 R₁₃ is -CH₂-O-Ar₁ and

 Ar₁ is 1-phenyl-3-trifluoromethyl-
pyrazole-5-yl wherein the phenyl is optionally
substituted with a chlorine atom;

or when

10 R₁₃ is -CH₂-O-CO-Ar₁, wherein

 Ar₁ is 2,6-dichlorophenyl.

2. The compound according to claim 1,
wherein:

X₁ is -CH;

15

g is 0;

J is -H;

m is 0 or 1 and T is -CO-CO₂H, or any bioisosteric
replacement for -CO₂H, or

20 m is 1 and T is -CO₂H;

ring C is benzo optionally substituted with
-C₁₋₃ alkyl, -O-C₁₋₃ alkyl, -Cl, -F or -CF₃;

R₅ is:

25

-CO-Ar₁

-SO₂-Ar₁,

-CO-NH₂,

-CO-NH-Ar₁

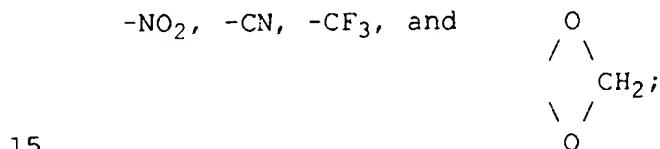
-CO-R₉,

- 758 -

each Q_1 is independently selected from the group consisting of:

- $-Ar_1$
 $-O-Ar_1$
 5 $-R_9$,
 $-T_1-R_9$, and
 $-(CH_2)_{1,2,3}-T_1-R_9$;

each Q_2 is independently selected from the group consisting of $-OH$, $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $-CF_3$, and



provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1 ;

each X is independently selected from the group consisting of $=N-$, and $=CH-$;

each X_2 is independently selected from the group consisting of $-O-$, $-CH_2-$, $-NH-$, $-S-$, $-SO-$, and $-SO_2-$;

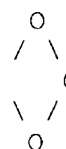
each Y is independently selected from the group consisting of $-O-$, $-S-$, and $-NH$;

provided that when

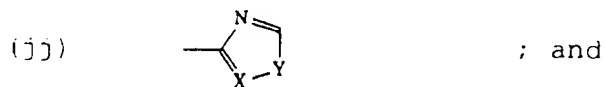
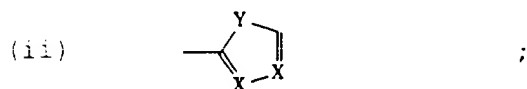
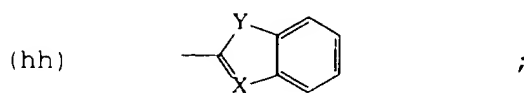
- g is 0,
 J is $-H$,
 m is 1,
 30 T is $-CO_2H$,

- 757 -

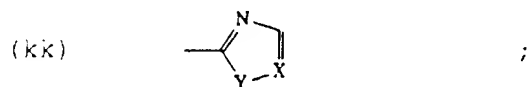
atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds,
 5 said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted with -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN,

10 =O, -OH, -perfluoro C₁₋₃ alkyl,  CH₂, or -Q₁;

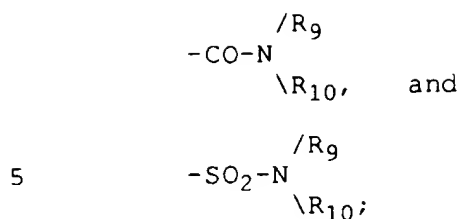
each Ar₂ is independently selected from the
 15 following group, in which any ring may optionally be singly or multiply substituted by -Q₁ and -Q₂:



20



- 756 -



10 R_6 is:
 -H
 -Ar₁,
 -R₉,
 -(CH₂)_{1,2,3}-T₁-R₉, or
 an α-amino acid side chain residue;

15 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, or =O and optionally substituted with one or two Ar₁ groups;

each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

20 each R₁₃ is independently selected from the group consisting of -Ar₂, -R₄ and $\begin{array}{c} \text{-N-OH} \\ \backslash \\ \text{R}_5; \end{array}$

25 each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a
 30 heterocycle group containing between 5 and 15 ring

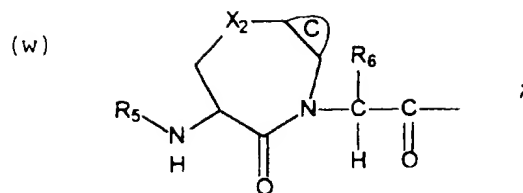
- 755 -

-S-,
 -SO-,
 -SO₂-,
 -NR₁₀-,
 5 -NR₁₀-CO-,
 -CO-,
 -O-CO-,
 -CO-O-,
 -CO-NR₁₀-,
 10 -O-CO-NR₁₀-,
 -NR₁₀-CO-O-,
 -NR₁₀-CO-NR₁₀-,
 -SO₂-NR₁₀-,
 -NR₁₀-SO₂-, and
 15 -NR₁₀-SO₂-NR₁₀-;

each R₅ is independently selected from the group consisting of:

-H,
 -Ar₁,
 20 -CO-Ar₁,
 -SO₂-Ar₁,
 -CO-NH₂,
 -SO₂-NH₂,
 -R₉,
 25 -CO-R₉,
 -CO-O-R₉,
 -SO₂-R₉,
 /Ar₁
 -CO-N
 30 \R₁₀,
 /Ar₁
 -SO₂-N
 \R₁₀,

- 754 -



wherein each ring C is independently chosen from
the group consisting of benzo, pyrido, thieno, pyrrolo,
5 furano, thiazolo, isothiazolo, oxazolo, isoxazolo,
pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R₃ is:

- CN,
- CH=CH-R₉,
- 10 -CH=N-O-R₉,
- (CH₂)₁₋₃-T₁-R₉,
- CJ₂-R₉,
- CO-R₁₃, or
- 15 -CO-CO-N
 /R₅
 \R₁₀;

each R₄ is independently selected from the group
consisting of:

- H,
- 20 -Ar₁,
- R₉,
- T₁-R₉, and
- (CH₂)_{1,2,3}-T₁-R₉;

each T₁ is independently selected from the group
25 consisting of:

- CH=CH-,
- O-,

- 753 -

CLAIMS

We claim:

1. A compound represented by the formula:



wherein:

10 X_1 is -CH; g is 0 or 1;

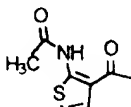

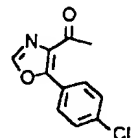

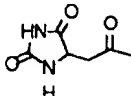

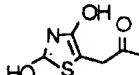

each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is
 15 -OH, said second J is -H;

 m is 0, 1, or 2;

T is -OH, -CO-CO₂H, -CO₂H, or any bioisosteric replacement for -CO₂H;

20 R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1 , at any nitrogen by R_5 , or at any atom by =O, -OH, -CO₂H, or halogen; and any saturated ring may optionally be unsaturated at one or two bonds;

- 752 -

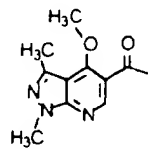
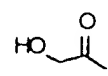
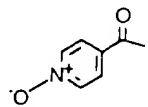
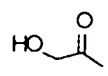
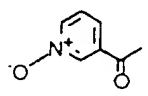
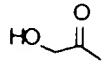
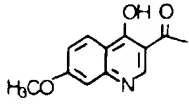
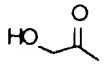
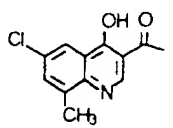
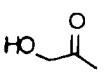
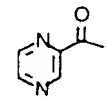
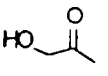
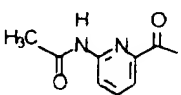
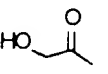
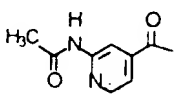
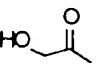
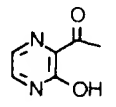
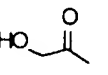
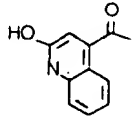
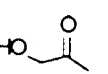
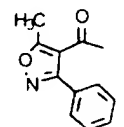
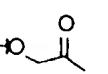
Compound	R ⁴	R ³
764		
765		
766		
767		

5 The data of the examples above demonstrate that compounds according to this invention display inhibitory activity towards IL-1 β Converting Enzyme.

Insofar as the compounds of this invention are able to inhibit ICE in vitro and furthermore, may be
 10 delivered orally to mammals, they are of evident clinical utility for the treatment of IL-1-, apoptosis-, IGIF-, and IFN- γ mediated diseases. These tests are predictive of the compounds ability to inhibit ICE in vivo.

15 While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope
 20 of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

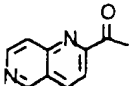

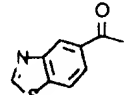

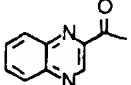

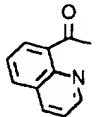

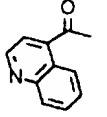

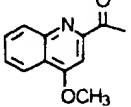

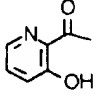

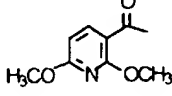

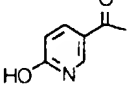

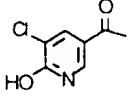

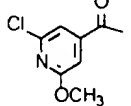

- 751 -

Compound	R ⁴	R ³
753		
754		
755		
756		
757		
758		
759		
760		
761		
762		
763		

5

10

- 750 -

Compound	R ⁴	R ³
742		
743		
744		
745		
746		
747		
748		
749		
750		
751		
752		

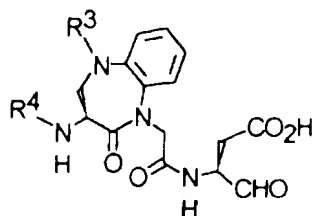
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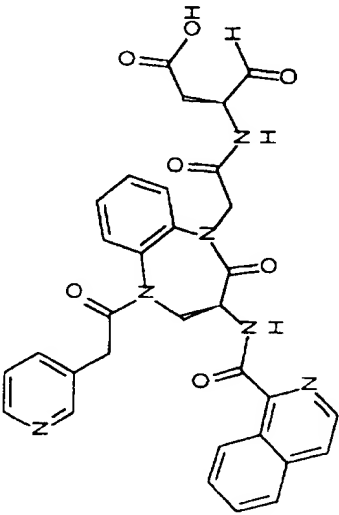
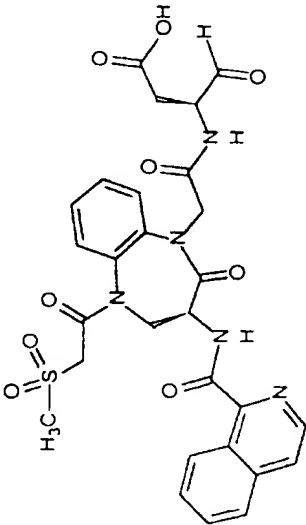
- 749 -

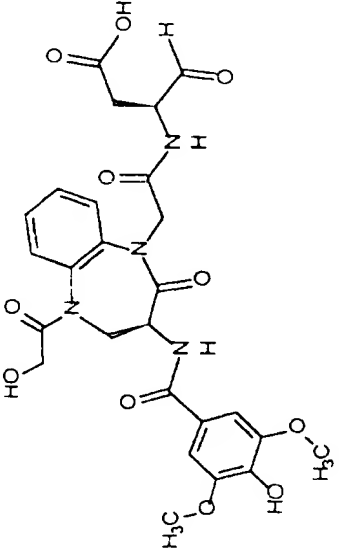
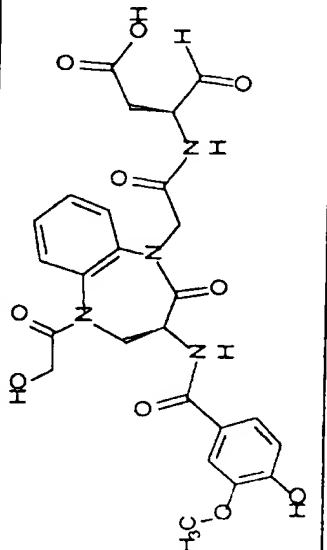
Example 35

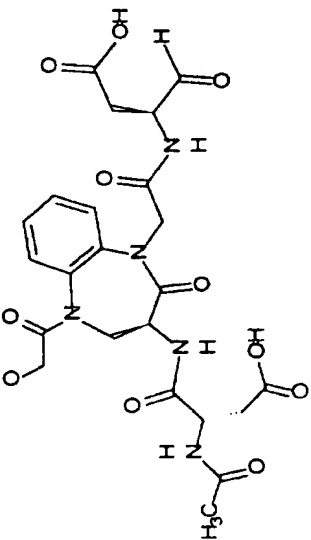
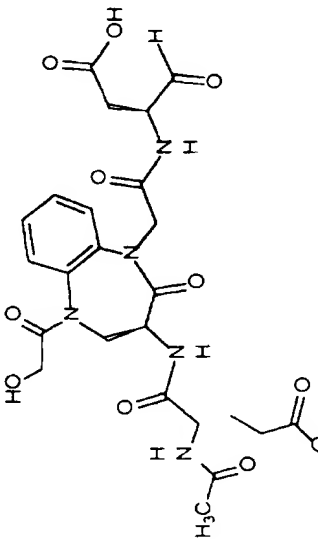
Compounds 736-767 were prepared by methods similar to the methods used to prepare compounds 619-635 (see, Example 13). Physical data for compounds 736-767 is listed in Table 30.

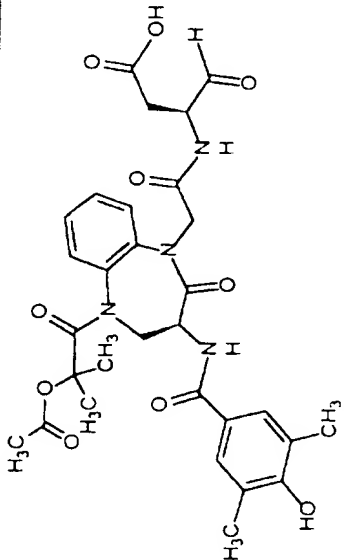
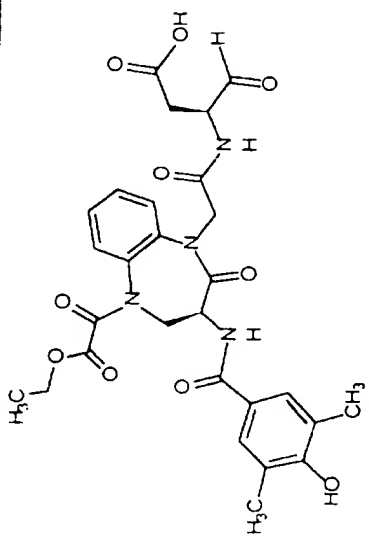
Table 30

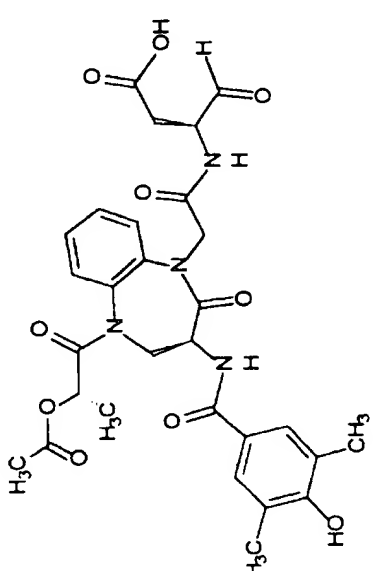
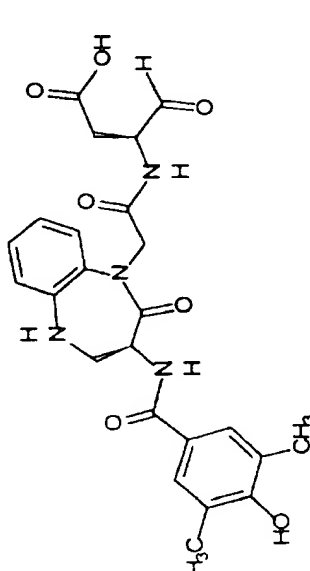
Compound	R ⁴	R ³
736		
737		
738		
739		
740		
741		

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) ⁺
734		C32H28N6O7	608.62	9.656 99%	630.6
735		C28H27N5O9S	609.62	10.887 92%	632.1

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) ⁺
732		C26H28N4O11	572.53	7.640 98%	595.9
733		C25H26N4O10	542.51	7.375 98%	565.9

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) ⁺
730		C23H27N5O11	549.50	3.939 96%	572.2
731		C24H29N5O11	563.53	4.298 92%	587

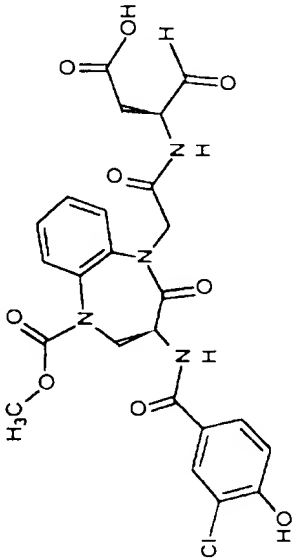
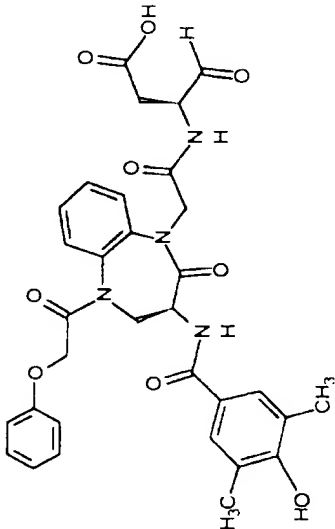
Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
728		C30H34N4O10	610.63	11.556	634.9
729		C28H30N4O10	582.57	11.611 99%	607.3

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) ⁺
726		C29H32N4O10	596.60	10.667 99%	620.8
727		C24H26N4O7	482.50	9.085 92%	506.6

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
724		C27H30N4O8	538.56	10.584 99%	563.1
725		C28H32N4O8	552.59	11.329 99%	577.2

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) ⁺
722		C27H30N4O9	554.56	11.761 99%	578.2
723		C26H28N4O9	540.53	10.655 79%	564.5

Table 29

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) ⁺
720		C ₂₄ H ₂₃ Cl ₄ N ₄ O ₉	546.93	10.729 99%	568.8
721		C ₃₂ H ₃₂ N ₄ O ₉	616.63	13.241 99%	640.4

- 740 -

Example 34

Compounds 720-73 were prepared by methods similar to the methods used to prepare compounds 619-635 (see, Example 13). Physical data for compounds
5 720-73 is listed in Table 29.

- 739 -

1H), 7.82 (t, 1H), 8.05 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid, O-2,6-dichlorobenzyl oxime (688c) was synthesized via methods used to prepare 308d to afford 800, ¹H NMR (CD₃OD) δ 2.2 (s, 6H), 2.58-2.83 (m, 2H), 3.28 (s, 3H), 3.29-3.34 (m, 1H), 3.68-3.80 (m, 2H), 3.95-4.05 (dd, 1H), 4.38-4.48 (dd, 1H), 4.82-5.00 (m, 2H), 5.26-5.36 (m, 2H), 7.22-7.65 (m, 10H).

(3S)-2-Oxo-(2,4-dimethylthiazo-5-yl)amino-5-hydroxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (800) was synthesized via methods used to prepare 696a-1 to afford 204 mg of 800 as a yellow solid, ¹H NMR (CDCl₃) (mixture of diastereomers) δ 1.70 (s, 1H), 2.40-2.80 (m, 7H), 2.80-2.90 (m, 0.5H), 2.95-3.05 (m, 0.5H), 3.30-3.35 (m, 0.5H), 3.45-3.55 (m, 0.5H), 3.55-3.65 (m, 1H), 3.80-4.05 (m, 2H), 4.30-4.50 (m, 2H), 4.55-4.65 (m, 1H), 4.75-4.95 (m, 3H), 5.45 (s, 0.5H), 5.55 (d, 0.5H), 6.70 (d, 0.5H), 6.90 (d, 0.5H), 7.15-7.80 (m, 10H)

(3S)-3-[(3S)-2-Oxo-3-(2,4-dimethylthiazo-1-oyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (801) was synthesized via methods used to prepare 2002 from 2001 to afford 801.

- 738 -

(m, 3H), 7.65 (m, 1H), 7.75 (t, 1H), 7.85 (t, 1H), 8.00 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-ylamino-5-hydroxyacetyl-2,3,4,5-tetrahydro-7-chloro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxobutyric acid(696-2)
5 was synthesized via methods used to prepare 2002 from 2001 to afford 250 mg of 696-2 as a white solid, ¹H NMR(CD₃OD) δ 2.40-2.55(m, 1H), 2.60-2.75(m, 1H), 3.80-4.00(m, 2H), 4.05(d, 1H), 4.20-4.35(m, 1H), 4.45-
10 4.65(m, 3H), 4.80-5.10(m, 2H)

(3S)-2-Oxo-3-isoquinolin-1-ylamino-5-methoxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(699a-1) was synthesized via methods used to
15 prepare 655 to afford 699a-1 ¹H NMR (500 MHz, CDCl₃) δ 2.55 (ddd, 1H), 2.90 (ddd, 1H), 3.25 (s, 3H), 3.28 (s, 3H), 3.80 (bt, 2H), 3.95 (bm, 2H), 4.25 (dd, 1H), 4.45-4.90 (m, 3H), 5.60 (d, 1H), 7.05- 7.40 (m, 8H), 7.50 (bm, 1H), 7.65- 7.85 (m, 2H), 8.45 (d, 1H), 9.1 (m,
20 1H), and 9.35 ppm (m, 1H)

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-ylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxobutyric acid(699a-2)
25 was synthesized via methods used to prepare 2002 from 2001 to afford 699a-2 ¹H NMR (500 MHz, CD₃OD) δ 2.51 (m, 1H), 2.70 (dt, 1H), 3.31 (bs, 3H), 3.90 (bdt, 1H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.35 (m, 1H), 4.50 (d, 1H), 4.60 (dd, 1H), 4.65 (dt, 1H), 4.80 (m, 1H), 5.05 (m, 1H), 7.35- 7.48 (m, 3H), 7.65 (bm, 1H), 7.75 (t,

- 737 -

(d, 1H), 7.10 (d, 1H), 7.20-7.35 (m, 3H), 7.40- 7.50 (m, 1H), 7.60- 7.85 (m, 3H), 8.40 (dd, 1H), 9.10 (m, 1H), and 9.30 pp (m, 1H).

(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-N-
5 [(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-
2,3,4,5-tetrahydro-7-chloro-1H-1,5-benzodiazepine-1-
acetamide (696a-2) was synthesized via methods used to
prepare 677, to afford 204 mg of 696a-2 as a white
solid, with the exception that the reduction of the
10 nitro- group was done as follows: To a solution of the
nitro compound (7.2 g, 20 mmol) in MeOH was added NH_4Cl
(2.1 g, 39 mmol) and Zn (17 g, 260 mmol). The
resulting mixture was heated to reflux 1 hour after
which it was cooled and filtered through celite. The
15 filtrate was concentrated *in vacuo* then treated with
cold 1N HCl to afford 3.6 g of a pale red solid. ^1H
NMR(CDCl_3) δ 1.85(s, 1H), 2.45(d, 0.5H), 2.50-2.65(m,
0.5H), 2.80-2.90(m, 0.5H), 2.90-3.00(m, 0.5H), 3.45(s,
0.5H), 3.55-3.75(m, 1H), 3.85-4.15(m, 2H), 4.25(d, 1H),
20 4.40-4.65(m, 2H), 4.70-4.80(m, 0.5H), 4.85-5.15(m, 3H),
5.40(s, 0.5H), 5.60(d, 0.5H), 7.00(d, 0.5H), 7.15-
7.90(m, 12.5H), 8.35-8.45(m, 1H), 9.00-9.10(m, 1H),
9.25-9.40(m, 1H)

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-
25 hydroxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-
benzodiazepine-1-acetylamino]4-oxobutyric acid (696-1)
was synthesized via methods used to prepare 2002 from
2001 to afford 140 mg of 696-1 as a white solid, ^1H NMR
(500 MHz, CD_3OD) δ 2.50 (m, 1H), 2.70 (m, 1H), 3.85 (d,
30 1H), 3.95 (m, 1H), 4.10 (d, 1H), 4.35 (m, 1H), 4.50-
4.60 (m, 2H), 4.80 (bm, 1H), 5.00 (m, 1H), 7.40- 7.48

- 736 -

4.85 (m, 1H), 4.88-5.1 (m, 2H), 5.45 (s, 0.5H), 5.55-5.65 (d, 0.5H), 6.85-6.92 (m, 1H), 7.02-7.13 (m, 2H), 7.24-7.55 (m, 9H).

5 (3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (689b-1) was synthesized via methods used to prepare 2002 from 2001 to afford
10 689b-1, ¹H NMR (CD₃OD) δ 2.18 (s, 6H), 2.36-2.47 (m, 1H), 2.6-2.72 (m, 1H), 3.34 (s, 3H), 3.66-3.88 (m, 2H), 3.95-4.05 (m, 1H), 4.2-4.78 (m, 5H), 4.9 (m, 1H), 7.3-7.41 (m, 2H), 7.48 (s, 2H), 7.5-7.63 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (699) was synthesized via methods used to prepare 2002 from 2001 to afford
15 699 as a white solid, ¹H NMR (500 MHz, CD₃OD) δ 2.50 (m, 1H), 2.70 (m, 1H), 3.25 (s, 3H), 3.80 (bd, 1H),
20 3.90 (bd, 1H), 4.00 (bd, 1H), 4.30 (m, 1H), 4.50-4.70 (m, 3H), 4.80-4.85 (bt, 1H), 5.00 (bm, 1H), 7.40-7.55 (m, 5H), 7.70 (bm, 1H), 7.85 (bm, 1H), 8.00 (bm, 1H), 8.55 (bd, 1H), and 9.05 ppm (bd, 1H).

(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-N-
25 [(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide (696a-1) was synthesized via methods used to prepare 656 to afford 800 as a yellow solid, ¹H NMR (500 MHz, CDCl₃) δ 2.55 (ddd, 1H), 2.85 (ddd, 1H),
30 3.70-3.80 (m, 2H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.30 (d, 1H), 4.40-4.60 (m, 4H), 4.70-5.05 (m, 4H), 5.55

- 735 -

1H), 7.3-7.85(m, 11H), 7.9(t, 1H), 8.2(d, 1H), 8.6(m, 1H), 9.3(m, 1H).

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-

5 **acetyl amino]4-oxobutyric acid(698)** was synthesized via methods used to prepare 653 to afford 225 mg of 698 ¹H NMR (500 MHz, CD₃OD) δ 2.4(m, 1H), 2.6(m, 1H), 3.9(m, 1H), 4.2(m, 1H), 4.3-4.7(m, 4H), 5.1(m, 1H), 7.3-7.5(m, 4H), 7.6-7.8(m, 2H), 7.8(m, 2H), 8.2(d, 1H), 8.5(d, 10 1H), 9.0(d, 1H).

(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-

acetamide(699a) was synthesized via methods used to 15 prepare 655 to afford 820 mg of 699a as a tan solid, ¹H NMR (500 MHz, CDCl₃) δ 2.60 (ddd, 1H), 2.90 (ddd, 1H), 3.20 (s, 3H), 3.25 (s, 3H), 3.70 (t, 1H), 3.90 (m, 2H), 4.20 (dd, 1H), 4.60 (m, 2H), 4.70-5.00 (m, 5H), 5.55 (d, 1H), 7.00 (d, 1H), 7.20-7.50 (m, 7H), 8.45 (dd, 20 1H), 9.0 (dd, 1H), and 9.35 ppm (dd, 1H).

(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(688b-1) was synthesized

25 via methods used to prepare 655 to afford 600 mg of 688b-1, ¹H NMR (CDCl₃; mix. of diastereomers) δ 2.21 (s, 3H), 2.28 (s, 3H), 2.42-2.50 (m, 0.5 H), 2.58-2.65 (m, 0.5H), 2.83-2.91 (m, 0.5H), 2.98-3.1 (m, 0.5H), 3.18 (s, 1.5H), 3.22 (s, 1.5H), 3.72-3.78 (d, 1H), 3.78-30 3.9 (m, 2H), 4.08-4.15 (d, 1H), 4.5-4.69 (m, 3H), 4.7-

- 734 -

2.6-2.7 (m, 0.5H), 2.8-2.9 (m, 0.5H), 2.92-3.03 (m, 0.5H), 3.55-3.8 (m, 2H), 3.92-4.02 (d, 1H), 4.25-4.3 (d, 0.5H), 4.37-4.42 (d, 0.5H), 4.43-4.48 (m, 0.5H), 4.55-4.65 (m, 1.5H) 4.7-5.12 (m, 5H), 5.44 (s, 0.5H),
5 5.58-5.63 (d, 0.5H), 6.95-8.1 (m, 13H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-aminobenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (697) was synthesized via methods used to prepare 2002 from 2001 to afford 140 mg
10 of 697, ¹H NMR (CD₃OD) δ 2.38-2.5 (m, 1H), 2.55-2.75 (m, 1H), 3.68-3.9 (m, 3H), 3.95-4.03 (m, 1H), 4.2-4.3 (m, 1H), 4.4-4.7 (m, 4H), 7.35-7.8 (m, 6H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-acetoxy-3-butenic acid ethyl ester (684a), was
15 synthesized by the methods used to prepare 2100j to afford 684a, ¹H NMR (500 MHz, CDCl₃ mixture of diastereomers) δ 1.3 (s, 9H), 1.8 (s, 3H), 2.1 (s, 3H), 2.15 (s, 3H), 2.3 (s, 6H), 3.3-3.5 (m, 3H), 3.65 (s, 3H), 3.9 (m, 1H), 4.1 (d, 1H), 4.3 (d, 1H), 4.6-4.8 (m, 3H), 5.0 (m, 1H), 6.7 (s, 1H), 7.0 (d, 1H), 7.1 (d, 1H), 7.2-7.5 (m, 6H).

(3S)-2-Oxo-3-isoquinolin-1-ylamino-5-formyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (698a) was synthesized via methods used to
25 prepare 652 to afford 795 mg of 698a ¹H NMR (500 MHz, CDCl₃ mixture of diastereomers) δ 2.8 (m, 2H), 4.0 (m, 1H), 4.5-4.8 (m, 4H), 5.2 (m, 1H), 5.5 (s, 1H), 5.75 (d,
30

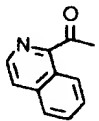

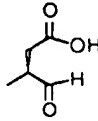
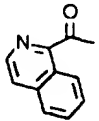

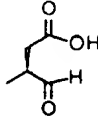
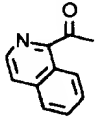

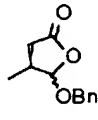
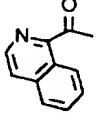

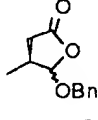
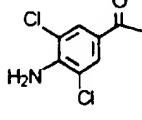

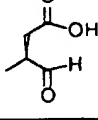
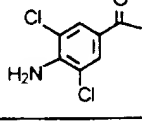

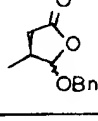
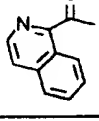

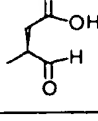
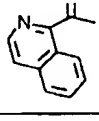

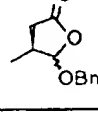
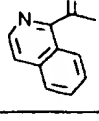
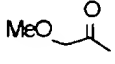
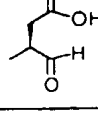
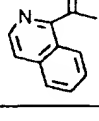
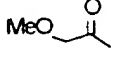
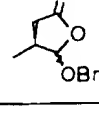
- 733 -

CIP#	R ⁴	R ³	R ⁵	R ¹
699a-1			F	
699a-2			F	
800			H	
801			H	

5 (3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4,4-diethoxybutyric acid ethyl ester (690a-1), was synthesized by the methods used to prepare 690a and
 10 2100b to afford 690a-1, ¹H NMR(CDCl₃) δ 1.15(t, 6H), 1.3(t, 3H), 2.25(s, 6H), 2.60(d, 2H), 3.50(m, 2H), 3.70(m, 4H), 4.05(m, 2H), 4.15(m, 2H), 4.30(d, 1H), 4.45(m, 1H), 4.50(d, 1H), 4.55(d, 1H), 4.70(t, 1H), 5.05(m, 1H), 5.30(s, 1H), 6.70(d, 1H), 7.10(d, 2H),
 15 7.30-7.50(m, 7H)

(3S)-2-Oxo-3-(3,5-dichloro-4-aminobenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (697a) was synthesized via
 20 methods used to prepare 677 to afford 840 mg of 697a, ¹H NMR (CDCl₃) δ 1.78 (br. s, 2H), 2.48-2.58 (d, 0.5H),

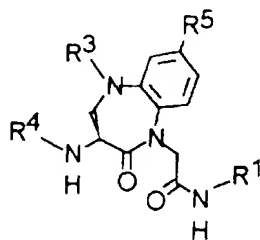
- 732 -

	CIP#	R ⁴	R ³	R ⁵	R ¹
	696-1			F	
	696-2			Cl	
	696a-2			Cl	
	696a-1			F	
5	697			H	
	697a			H	
	698			H	
	698a			H	
	699			H	
10	699a			H	

- 731 -

Example 33

Compounds 684a, 688b-1, 688c, 689b-1, 690a-1, 696-1, 696-2, 696a-2, 696a-1, 697, 697a, 698, 698a, 699, 699a, 699a-1, 699a-2, 800 and 801 were prepared as described below.

Table 28

CIP#	R ⁴	R ³	R ⁵	R ¹
684a			H	
688b-1			F	
688c			H	
689b-1			F	
690a-1			H	

- 730 -

Example 32Table 27

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	688c	200				
5	689b-1	3.5		2700		
	696-1	0.5				
	696-2	0.5				
	697	1.8		5000		
	698	18		13500		
10	699	1.1				
	699a-2					
	720	2.7				
	721	1.3		5000		
	722	5		5000		
15	723	2.3		2000		
	724	2		1800		
	725	3.7		3000		
	726	300				
	727	50		2300		
20	728	300				
	729	28		2800		
	730	90		8000		
	731	150				
	732	5		1800		
25	733	5		1500		
	734	9		6000		
	735	6		10000		

- 729 -

3.05(m, 1H), 3.9(d, 1H), 4.2(m, 1H), 4.3(d, 1H), 4.7-5.0(m, 3H), 5.25(m, 1H), 5.7(s, 1H), 5.9(d, 1H), 7.5(d, 2H), 7.7-7.9(m, 3H), 8.0(t, 1H), 8.2(m, 2H), 8.75(d, 1H), 9.35(d, 1H).

- 5 (3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-(2*RS*-cyclopentyloxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carboxamide (696d) was synthesized from 600b via methods used to prepare 690a from 600b to afford 696d. ¹H NMR (CDCl₃) δ
- 10 0.9(t, 1H), 1.2(t, 1H), 1.3-1.45(m, 2H), 1.6-1.8(m, 4H), 2.45(m, 1H), 2.8(m, 1H), 3.0(m, 1H), 3.4(q, 1H), 3.5(d, 1H), 4.0(m, 2H), 4.2-4.3(m, 2H), 4.55(d, 1H), 4.65(m, 1H), 4.9(m, 1H), 5.05(m, 1H), 5.4(s, 1H), 5.5(d, 1H), 6.8(d, 1H), 7.3-7.9(m, 6H), 8.5(d, 1H),
- 15 9.05(d, 1H), 9.4(d, 1H).

- (3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2*R*,3*S*)-phenethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (696e) was synthesized from 600b via methods used to
- 20 prepare 690a from 600b to afford 696e. ¹H NMR (CDCl₃) δ
- 1.2(t, 1H), 2.4(m, 1H), 2.8(m, 2H), 3.6(d, 1H), 3.7(q, 1H), 4.0(m, 2H), 4.3(d, 2H), 4.65(m, 1H), 4.85(t, 1H), 5.0(m, 1H), 5.35(d, 1H), 6.5(d, 1H), 7.15-7.85(m, 8H), 8.45(d, 1H), 9.05(d, 1H), 9.4(d, 1H).

- 728 -

(3S)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (696a) was synthesized from 600b via methods used to
5 prepare 690a from 600b to afford 696a. ¹H NMR (CDCl₃) δ 0.95(t, 2H), 1.25(t, 1H), 1.4(m, 2H), 1.55(m, 1H), 2.55(m, 1H), 2.85(m, 1H), 2.95(dd, 1H), 3.15(m, 1H), 3.55(m, 1H), 3.9(m, 2H), 4.35(t, 1H), 4.4-4.55(m, 2H), 4.75(m, 1H), 4.8-5.05(m, 2H), 5.45(s, 1H), 5.55(d, 1H),
10 6.85(d, 1H), 7.15(d, 1H), 7.2-7.5(m, 5H), 7.6-7.8(m, 3H), 8.45(d, 1H), 9.05(d, 1H), 9.35(d, 1H).

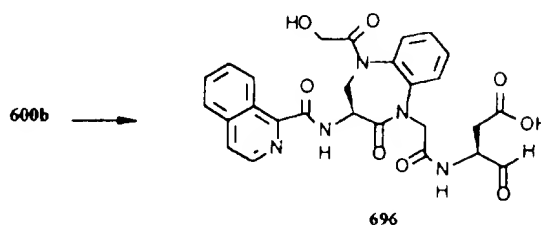
(3S)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696b)
15 was synthesized from 600b via methods used to prepare 690a from 600b to afford 696b. ¹H NMR (CDCl₃) δ 0.9(m, 3H), 1.15(q, 3H), 1.15(m, 1H), 1.65(m, 1H), 2.5(m, 1H), 2.8(m, 1H), 2.95-3.0(m, 2H), 3.6(m, 2H), 3.7-3.85(m, 4H), 4.0(m, 2H), 4.3(m, 1H), 4.55(m, 1H), 4.65(m, 1H),
20 4.85-4.95(m, 1H), 5.05(m, 1H), 5.35(s, 1H), 5.45(d, 1H), 6.85(d, 1H), 7.25(d, 1H), 7.35-7.85(6H), 8.85(dd, 2H), 9.05(m, 1H), 9.35(dd, 2H).

(3S)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-[2RS-(4-chlorobenzyl)oxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696c) was synthesized from 600b via methods used to
25 prepare 690a from 600b to afford 696c. ¹H NMR (CD₃OD) δ 1.25(t, 1H), 1.65(q, 1H), 1.9(m, 1H), 2.9(m, 1H),

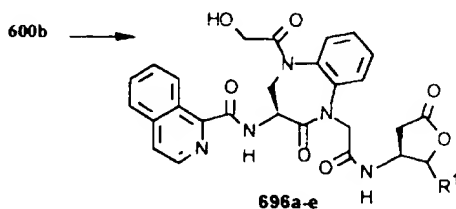
- 727 -


(2) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm).

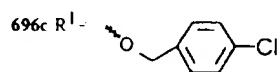
Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.




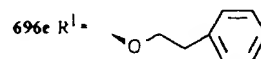
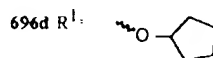
(3S)-3-[(3S)-2-Oxo-3-(isoquinolin-1-yl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (696) was synthesized from 600b by the method used to prepare 691a from 600b to afford 696. ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.75(d, 1H), 3.95(q, 1H), 4.05(d, 1H), 4.3(m, 1H), 4.45-4.65(m, 2H), 5.05(m, 1H), 7.5-7.6(m, 3H), 7.7(t, 1H), 7.8(t, 1H), 7.98(t, 1H), 8.55(d, 1H), 9.1(d, 1H).



696a R¹ = 



696b R¹ = 



- 726 -

Step E. (910-922) Resin 906 was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBT in N-methylpyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methylpyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), 50% methanol in dichloromethane (5 X 1 mL) and dried in air. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H₂O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (2 X 1 mL), the combined filtrates were added to cold 1:1 ether:hexane (35 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in acetonitrile (0.5 mL) and H₂O (0.5 mL) and filtered through 0.45 micron microcentrifuge filters. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (10% - 50%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide 910-922.

25

Analytical HPLC methods:

(1) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm). Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

- 725 -

dimethylacetamide (4 X 20 mL) and dichloromethane (4 X 20 mL), and dried under nitrogen purge. Resin substitution was performed as described for 401 and determined to be $0.169 \text{ mmol g}^{-1}$.

5

Step C. Synthesis of 905. Resin 903 (7.54 g, 1.27 mmol) and dimedone (2.19 g, 15.6 mmol) were placed in a 100 mL round bottomed flask and freshly distilled anhydrous tetrahydrofuran (60 mL) was added.

10 Tetrakis(triphenylphosphine)palladium (0) (0.32 g, 0.28 mmol) was added and the nitrogen blanketed, sealed reaction was agitated for 15 h on a wrist action shaker. The resin was filtered, washed with dimethylacetamide (4 X 20 mL), dichloromethane (4 X 20

15 mL) and dimethylacetamide (1 X 20 mL). Sufficient dimethylacetamide was added to the resin to obtain a slurry followed by pyridine (1.5 mL, 18.5 mmol) and a solution of 904 (5.5 mmol) in dichloromethane (10 mL). The reaction was shaken under nitrogen for 8 h, then

20 filtered. The resin was washed with dimethylacetamide (5 X 20 mL) and dichloromethane (5 X 20 mL).

Step D. Synthesis of 906. This compound was prepared from resin 905 (0.24 g, 0.038 mmol) using an

25 Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 10 min followed by fresh reagent (1 mL) for 20 min to yield

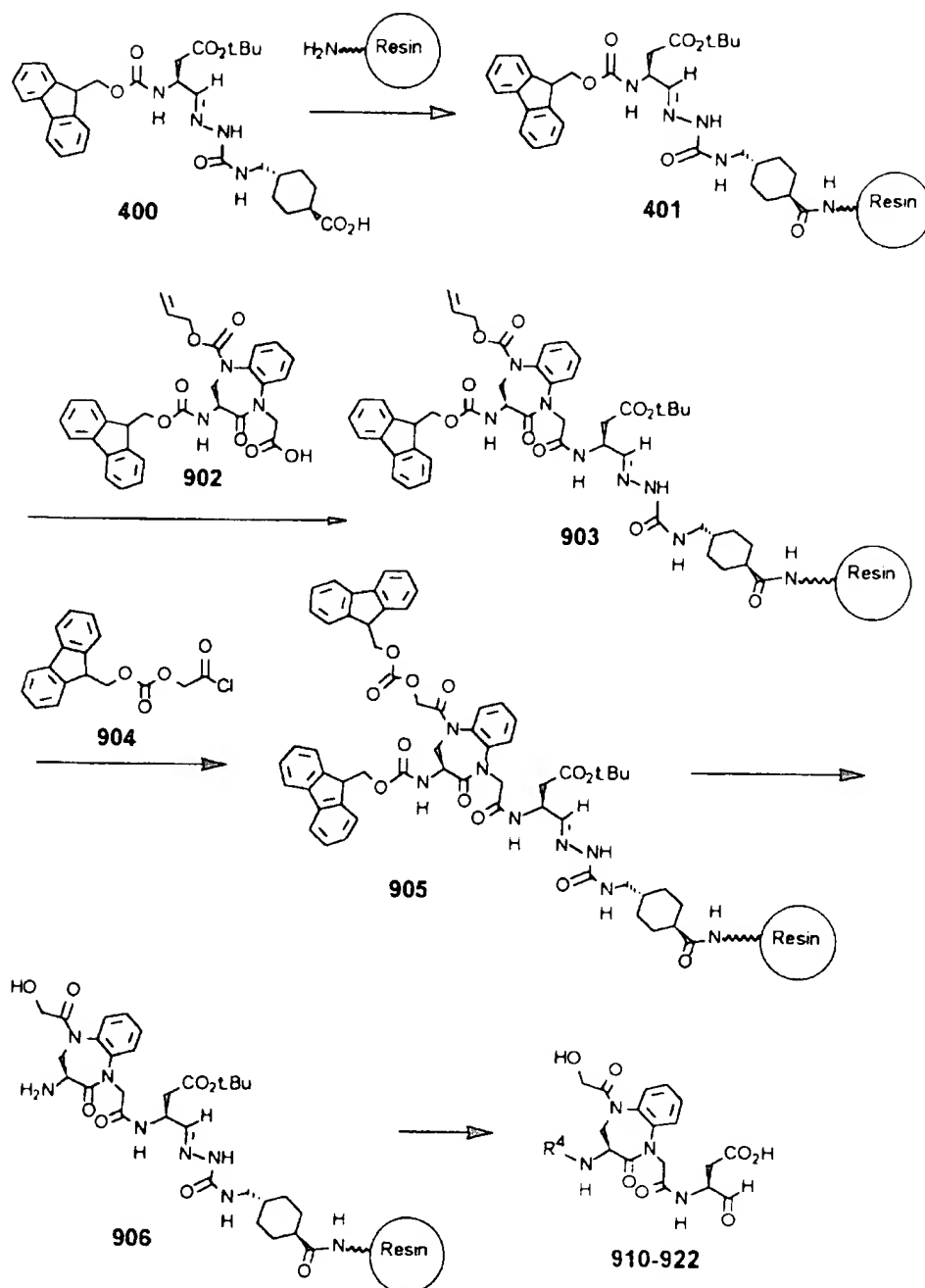
30 resin 906. The resin was washed with dimethylformamide (3 X 1 mL) and N-methylpyrrolidone (3 X 1 mL).

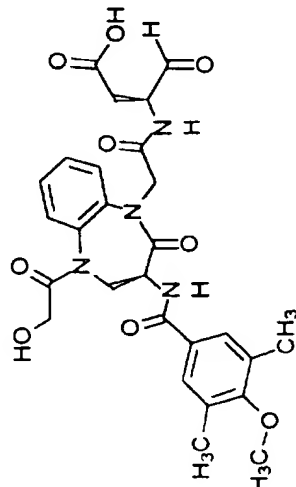
- 724 -

Step A. Synthesis of 401. TentaGel S@ NH₂ resin (0.25 mmol/g, 6.8 g) was placed in a glass shaker vessel and washed with dimethylacetamide (3 X 20 mL). To a solution of **400** (1.70 g, 2.9 mmol, prepared from
5 (3S) 3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)) in dimethylacetamide (15 mL) was added O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 1.09 g,
10 2.9 mmol), and DIEA (1.0 mL, 5.7 mmol). The solution was added to the resin, followed by dimethylacetamide (5 mL). The reaction mixture was agitated for 3 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with
15 dimethylacetamide (6 X 20 mL). A sample of resin (7.4 mg) was thoroughly washed with 50% methanol in dichloromethane and dried under suction. Deprotection of the Fmoc group using 20% piperidine in dimethylacetamide (10.0 mL) and UV analysis of the
20 solution revealed a substitution of 0.19 mmol g⁻¹.

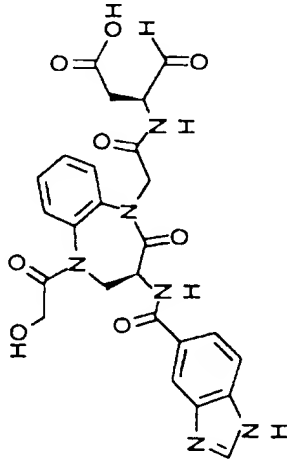
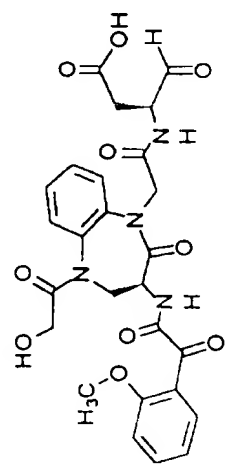
Step B. Synthesis of 903. Resin **401** was deprotected with 20% (v/v) piperidine/dimethylacetamide (20 mL) for 10 min (shaking) and then for 10 min with
25 fresh piperidine reagent (20 ml). The resin was then washed with dimethylacetamide (6 X 20 ml). A solution of **902** (1.52 g, 2.81 mmol) was treated with HBTU (1.07 g, 2.83 mmol) and DIEA (1.0 mL, 5.7 mmol) and transferred to the resin, followed by dimethylacetamide
30 (5 mL). The reaction mixture was agitated for 2.5 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with

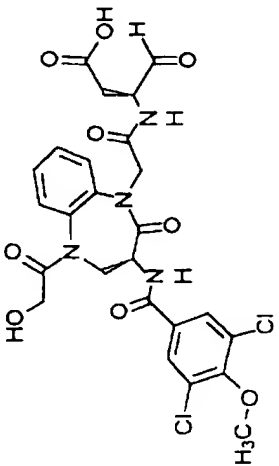
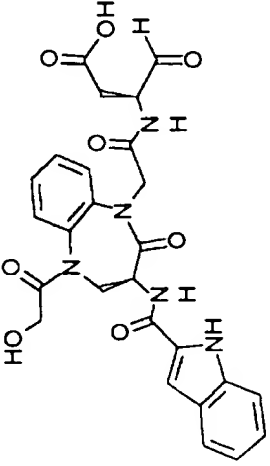
- 723 -



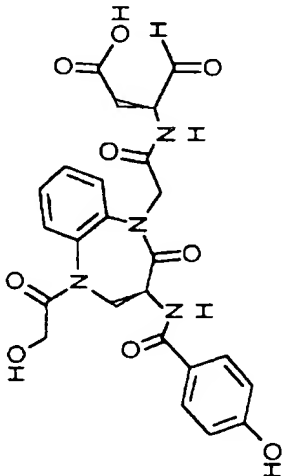
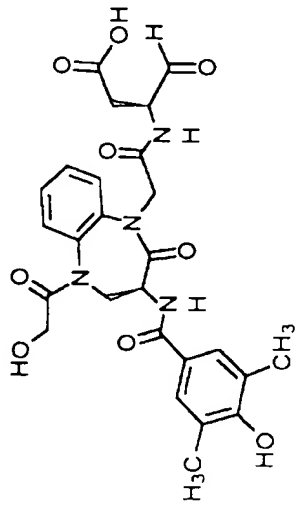
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
922/694		C27H30N4O9	554.56	10.024 (2) 99%	578.8

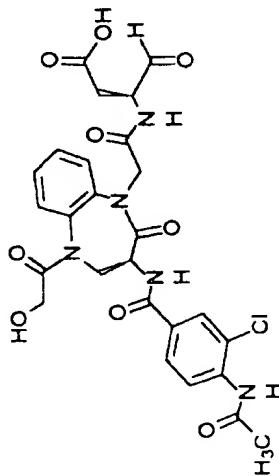
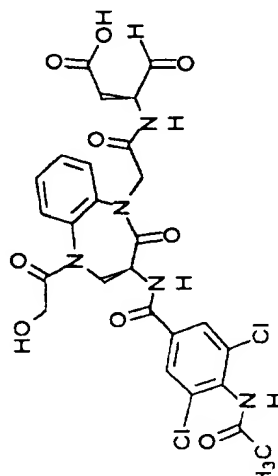
- 721 -

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
920		C25H24N6O8	536.51	5.494 (2) 98%	560.6
921		C26H26N4O10	554.52	7.827 (2) 96%	579.1

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
918		C25H24Cl2N4O9	595.40	11.817 (2) 99%	619.3
919		C26H25N5O8	535.52	9.709 (2) 91%	559.7

- 719 -

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
916/691b		C ₂₄ H ₂₄ N ₄ O ₉	512.48	6.331 (2) 98%	537
917/691a		C ₂₆ H ₂₈ N ₄ O ₉	540.53	8.114 (2) 99%	564.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
914		C26H26ClN5O9	587.98	7.815 (2) 99%	612.2
915		C26H25Cl2N5O9	622.42	7.490 (2) 98%	647

- 717 -

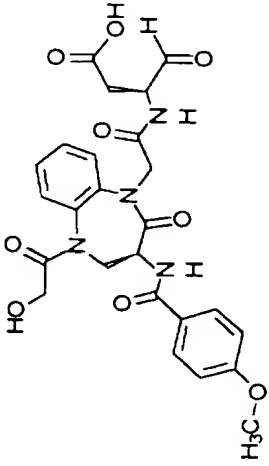
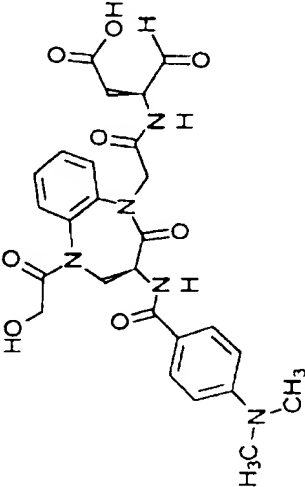
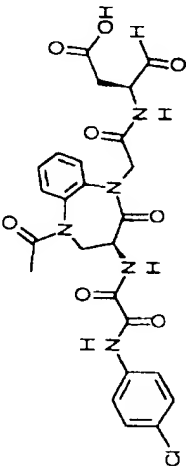
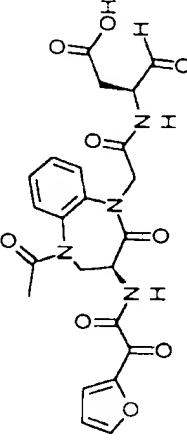
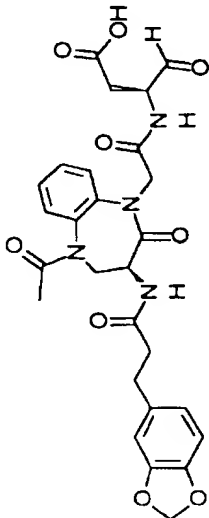
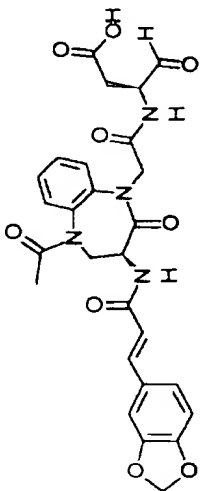
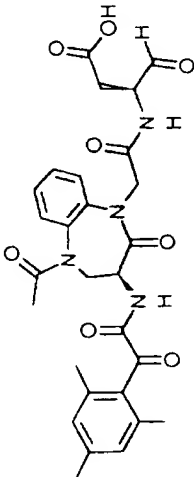
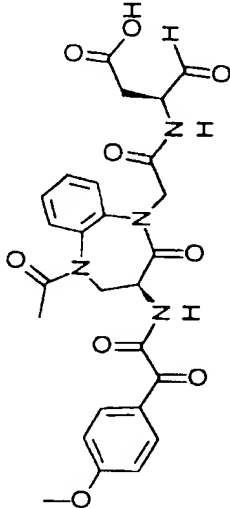
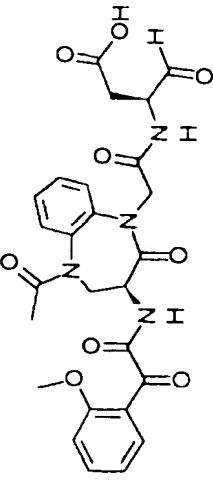
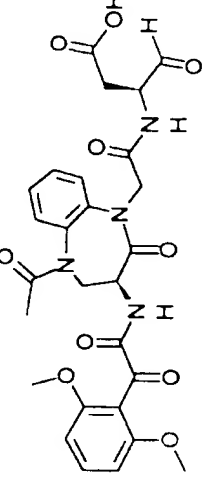
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
912		C25H26N4O9	526.51	8.317 (2) 99%	550.7
913		C26H29N5O8	539.55	6.588 (2) 99%	563.5

Table 26

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
910		C25H24N4O10	540.49	8.172 (2) 99%	564.4
911		C26H27N5O9	553.53	6.949 (2) 99%	577.5

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
710		C25H24ClN5O8	557.95	12.406 (2) 98%	582.2
711		C23H22N4O9	498.45	13.072 (1) 99%	521.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
707		C27H28N4O9	552.55	15.952 (1) 98%	575.9
708		C27H26N4O9	550.53	10.731 (2) 93%	574.6
709		C28H30N4O8	550.57	13.192 (2) 95%	574

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
704		C26H26N4O9	538.52	10.475 (2) 96%	562.1
705		C26H26N4O9	538.52	14.260 (1) 72%	562.1
706		C27H28N4O10	568.55	14.836 (1) 97%	592.4

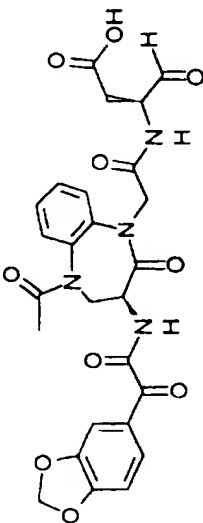
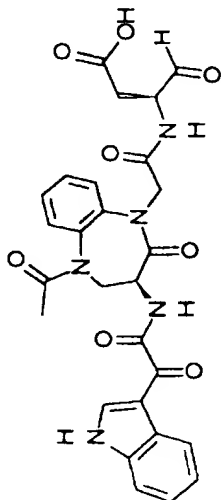
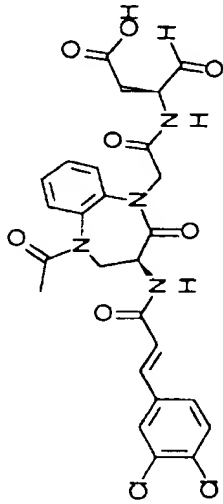
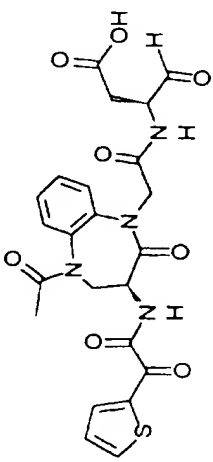
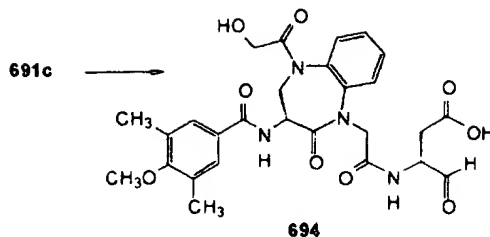
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) ⁺
702		C26H24N4O10	552.50	15.855 (1) 98%	575.9
703		C27H25N5O8	547.53	10.315 (2) 97%	572.1

Table 25

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) †
700		C26H24Cl2N4O7	575.41	14.061 (2) 97%	600
701		C23H22N4O8S	514.52	15.589 (1) 97%	538.8

- 710 -



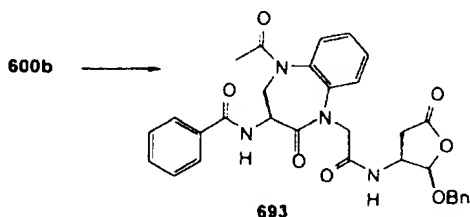
(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (**694**), was synthesized from **691c** by the method used to prepare **2002** from **2001** to afford 380 mg of **694** as a white solid, ^1H NMR (CD_3OD) δ 2.25(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.65(m, 5H), 4.0(d, 1H), 4.28(m, 1H), 4.55(d, 2H), 4.95(m, 1H), 7.4-7.6(m, 6H).

Compounds **700-711** were prepared by methods similar to the methods used to prepare compounds **619-635** (see, Example 13). Physical data for compounds **700-711** is listed in Table 25.

Compounds **910-915** and **918-921** were prepared as described below. Physical data for these compounds is listed in Table 26.

- 709 -

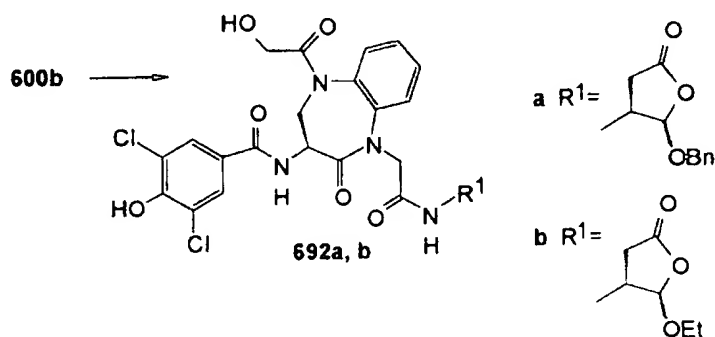
(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (692b), was synthesized from 600b via methods used to prepare 661 from 600b, excluding steps used to make 604d from 603d, using instead the method to prepare 688a from 687a to afford 207 mg of 692b, ¹H NMR (CD₃OD) δ 1.05(t, 3H), 1.15(t, 3H), 2.45(d, 1H), 2.55(m, 1H), 2.7(m, 1H), 3.55(m, 2H), 3.6-3.75(m, 5H), 4.0(dd, 2H), 4.3(d, 1H), 4.4-4.7(m, 5H), 5.25(s, 1H), 5.5(d, 1H), 7.25-7.6(m, 4H), 7.85(s, 2H).



(3S)-2-Oxo-3-benzoylamino-5-acetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (693), was synthesized from 600b via methods used to prepare 688a from 600b to afford 30 mg of 693, ¹H NMR (CD₃OD) δ 1.7(s, 3H), 1.8(s, 3H), 2.51(d, 1H), 2.6(m, 1H), 2.85(m, 1H), 3.0(m, 1H), 3.75(br. d, 2H), 4.0-4.1(dd, 2H), 4.5-5.0(m, 6H), 5.45(s, 1H), 5.55(s, 1H), 7.15-7.85(m, 14H).

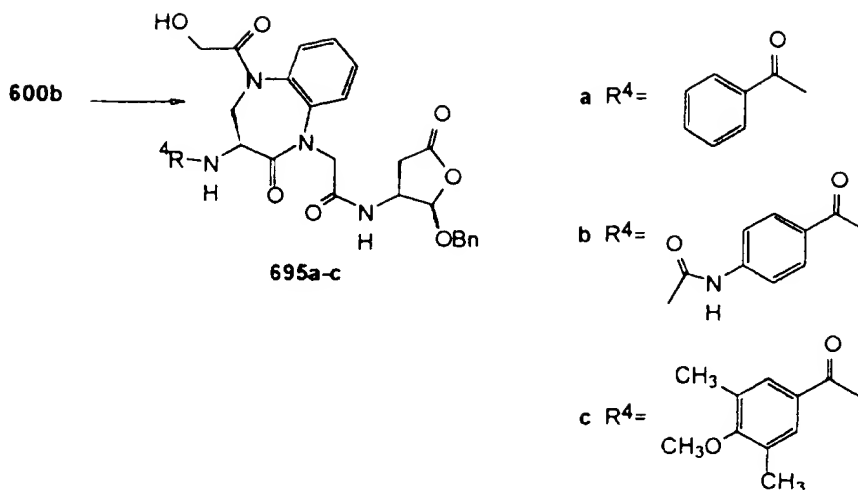
- 708 -

(3S)-2RS-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-(2-benzyloxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (**695c**), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 840 mg of **695c**,
¹H NMR(CDCl₃) δ 2.23(s, 3H), 2.26(s, 3H), 2.45-2.62(m, 1H), 2.8-2.9(dd, 0.5H), 2.9-3.05(dd, 0.5H), 3.45-3.63(m, 1H), 3.64(s, 1.5H), 3.68(s, 1.5H), 3.78-4.05(m, 2H), 4.2-4.33(m, 1H), 4.4-4.63(m, 2H), 4.65-4.94(m, 2H), 4.95-5.1(m, 1H), 5.45(s, 0.5H), 5.5-5.6(d, 0.5H), 6.9-6.95(d, 1H), 7.25-7.7(m, 12H).



(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (**692a**), was synthesized from **600b** via methods used to prepare **661** from **600b**, excluding steps used to make **604d** from **603d**, using instead the method to prepare **688a** from **687a** to afford 854 mg of **692a**,
¹H NMR (CD₃OD) δ 2.45(d, 1H), 2.6(m, 1H), 2.7(m, 1H), 3.0(m, 1H), 3.5-3.7(m, 4H), 4.0(q, 2H), 4.45(m, 3H), 4.55(m, 4H), 5.35(s, 1H), 5.6(d, 1H), 7.2-7.5(m, 9H), 7.85(s, 2H).

- 707 -



(3*S*)-2-Oxo-3-benzoylamino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**695a**), was synthesized from **600b** via methods used to prepare

5 **677** from **600b** to afford 75 mg of **695a**, ¹H NMR (CD₃OD) δ 2.2(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.65(m, 1H), 3.75(d, 1H), 4.0(d, 1H), 4.28(m, 1H), 4.5(m, 3H), 7.4-7.6(m, 6H).

(3*S*)-2-Oxo-3-(4-acetamidobenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**695b**), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 880 mg of **695b**, ¹H NMR (CDCl₃) δ 2.1(s, 3H), 2.25-2.5(m, 2H), 2.8-2.92(m, 0.5H), 3.15-3.2(m, 0.5H), 3.45-3.6(m, 2H), 3.75-3.95(m, 2H), 4.15-4.25(m, 1H), 4.35-4.6(m, 2H), 4.6-4.88(m, 3H), 5.22(s, 0.25H), 5.33(s, 0.25H), 5.52-5.58(d, 0.5H), 7.15-7.45(m, 9.5H), 7.5-7.75(m, 5H), 8.3-8.35(m, 0.5H), 9.08-9.18(m, 1H).

10

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- 706 -

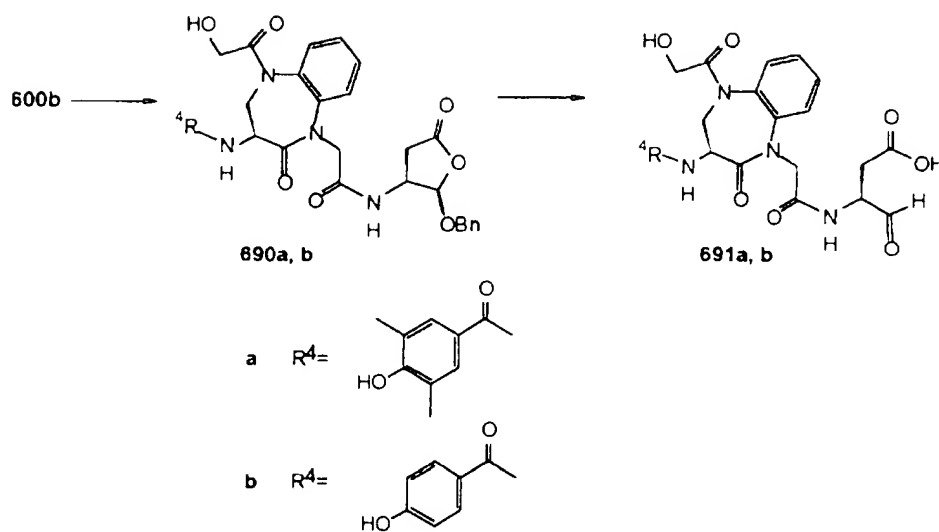
(CD₃OD) δ 2.49(d, 1H), 2.65(d, 1H), 2.66(d, 1H), 2.85(d, 1H), 2.87(d, 1H), 3.05(dd, 1H), 3.35(br. s, 1H), 3.72(br. s, 2H), 4.01(m, 2H), 4.45(br. m, 1H), 4.6(m, 1H), 4.7(m, 1H), 4.8(m, 1H), 4.95(br. s, 2H), 5.65(d, 1H), 6.8(d, 2H), 7.2-7.35(br. m, 3H), 7.45(m, 2H), 7.75(d, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyr
10 ic acid (691a), was synthesized from 690a by the method used to prepare 2002 from 2001 to afford 560 mg of 691a as a white solid, ¹H NMR (CD₃OD) δ 2.15(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.55(m, 1H), 3.7(d, 1H), 4.0(d, 1H), 4.25(m, 1H), 4.5-4.6(m, 3H), 7.3-7.5(m, 6H).
15

(3S)-3-[(3S)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyr
20 ic acid (691b), was synthesized from 690b by the method used to prepare 2002 from 2001 to afford 410 mg of 691b as a white solid, ¹H NMR (CD₃OD) δ 2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H), 3.8(d, 1H), 4.05(d, 1H), 4.25(m, 1H), 4.5(m, 1H), 4.6(m, 1H), 4.95(br. s, 2H), 6.8(d, 2H), 7.45(m, 2H), 7.6(m, 2H), 7.75(d, 2H).

- 705 -

2.7(m, 1H), 3.3(s, 3H), 3.7-3.85(m, 2H), 4.05(dd, 1H),
4.3(m, 1H), 4.6(m, 2H), 7.45-7.4(m, 2H), 7.5(s, 2H),
7.55(m, 2H).



(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (690a), was synthesized from 600b via methods used to prepare 676 from 600b, 688a from 687a, then 677 from 676 to afford 863 mg of 690a as a white solid, ^1H NMR (CD_3OD) δ 2.2(s, 6H), 2.45(d, 0.5H), 2.6-2.9(m, 1H), 3.05(dd, 0.5H), 3.65-3.85(m, 2H), 3.95-4.1(m, 1H), 4.35-5.0(m, 7H), 5.35(s, 0.5H), 5.65(d, 0.5H), 7.2-7.4(m, 4H), 7.4-7.7(m, 7H).

(3S)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (690b), was synthesized from 600b via methods used to prepare 677 from 600b to afford 200 mg of 690b, ^1H NMR

- 704 -

NMR (CD₃OD) δ 2.55(dd, 1H), 2.7(dd, 1H), 3.0(m, 1H), 3.6(m, 1H), 3.75(d, 1H), 3.9-4.0(m, 2H), 4.3-4.45(m, 3H), 4.5-4.6(m, 3H), 4.7(m, 2H), 5.35(s, 1H), 5.55(d, 1H), 7.1-7.5(m, 4H), 7.85(s, 2H).

5 (3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (688b), was synthesized from 687b by the method used to prepare 688a from 687a to
10 afford 960 mg of 688b as an off-white solid, ¹H NMR (CD₃OD) δ 2.6(dd, 1H), 2.7(dd, 1H), 3.0(dd, 1H), 3.2(s, 3H), 3.7(m, 3H), 3.9(m, 2H), 4.4-4.5(m, 2H), 4.6(m, 3H), 5.35(s, 1H), 5.55(d, 1H), 7.25(m, 2H), 7.4-7.5(m, 4H).

15 (3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (689a), was synthesized from 688a by the method used to prepare 2002 from 2001 to afford 184 mg
20 of 689a as a white solid, ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.6(m, 1H), 3.3(s, 3H), 3.7-3.85(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.5-4.6(m, 3H), 7.3-7.6(m, 4H), 7.85(s, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (689b), was synthesized from 688b by the method used to prepare 2002 from 2001 to afford 412 mg
25 of 689b as a white solid, ¹H NMR (CD₃OD) δ 2.5(m, 1H),

- 703 -

(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (687a), was synthesized from 600b using methods similar to those used for preparing 654 from 600b to afford 1.6 g of 687a.

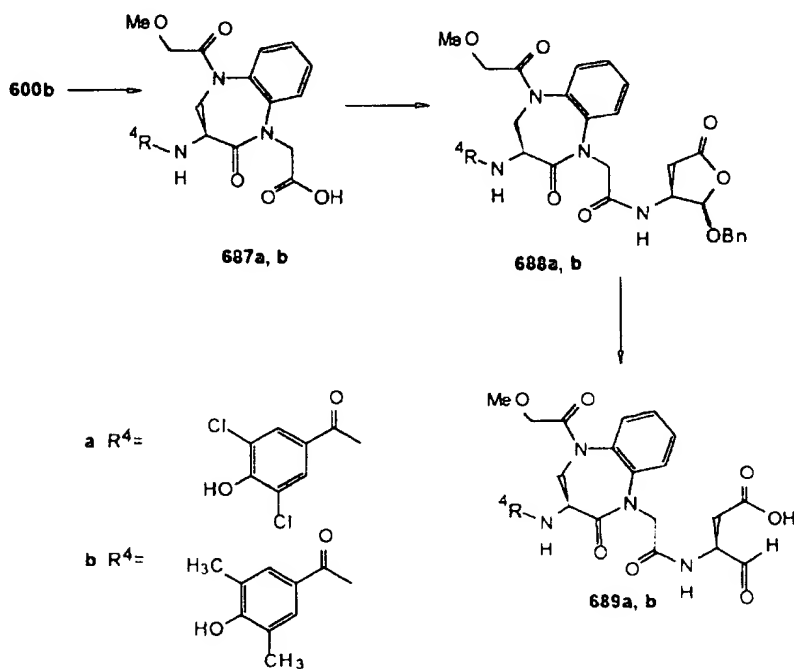
(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (687b), was synthesized from 600b using methods similar to those used for preparing 654 from 600b to afford 1.1 g of 687b.

(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (688a). To a solution of (3S,2R,S)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-618 (1992)) (1.13 g, 1.2 equiv) in CH₂Cl₂ was added triphenylphosphine (423 mg, 0.5 equiv), dimethylbarbituric acid (1.26 g, 2.5 equiv), and tetrakis(triphenylphosphine) palladium (0) (373 mg, 0.1 equiv). After 5 minutes the reaction mixture was cooled via ice-bath then added a solution of 687a in DMF (1.6 g, 1 equiv), HOBT (480 mg, 1.1 equiv), and EDC (681 mg, 1.1 equiv). The resulting mixture was allowed to stir at ambient temperature. After 16 hours the reaction mixture was poured into NaHSO₄ and extracted twice with EtOAc. The organic layer was washed with NaHCO₃, brine, dried over Na₂SO₄ and concentrated in vacuo. Chromatography (SiO₂, 20% to 100% EtOAc in CH₂Cl₂) afforded 880mg of 688a as an off-white solid, ¹H

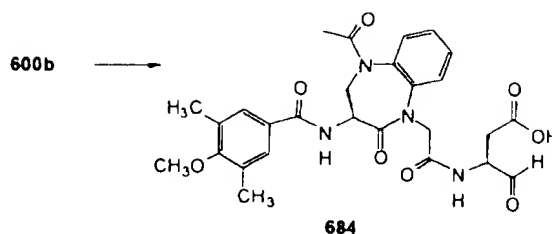
- 702 -

benzodiazepine-1-acetamide (**685**), was synthesized from **600b** by the methods used to prepare **676** from **600b** to afford 165 mg of **685**.

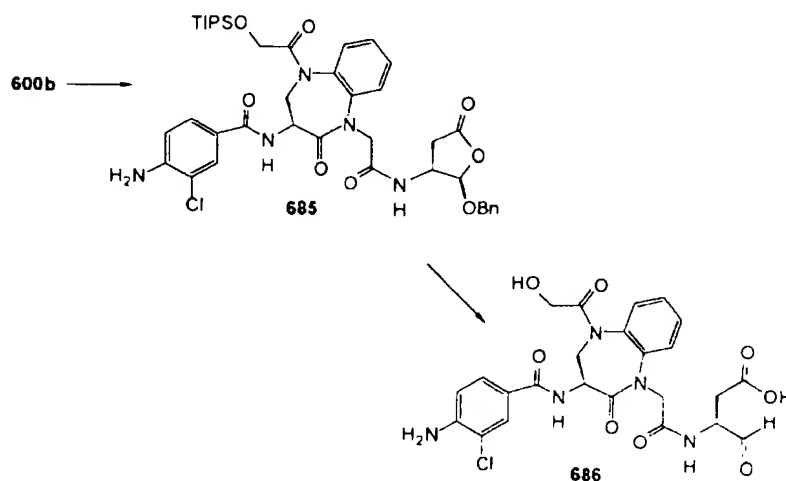
(3*S*)-3-[(3*S*)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyr-ic acid (**686**). To a solution of **685** (165 mg, 0.21 mmol) in THF was added a solution of TBAF (1*M*, 0.21 mL). The product was isolated by filtration after precipitation from reaction mixture. Reverse phase chromatography (10% to 80% MeCN in water/ 0.1% TFA) afforded 25 mg of **686** as a white solid, ^1H NMR (CD_3OD) δ 2.37-2.42 (m), 2.59-2.70 (m), 3.60-3.89 (m), 4.01 (d), 4.20-4.31 (m), 4.42-4.70 (m), 4.80-5.05 (m), 6.79 (d), 7.32-7.65 (m), 7.81 (s).



- 701 -



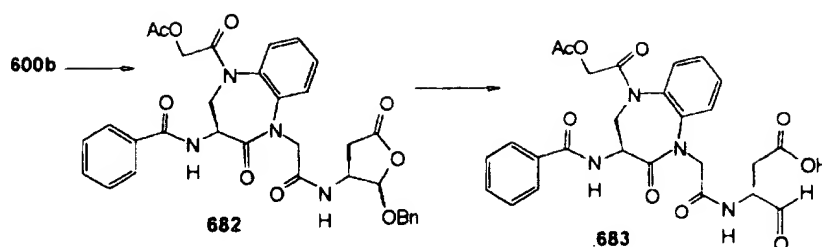
(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylaminol]4-oxo-butyrac acid (**684**), was synthesized from **600b** by the method used to
 5 prepare **605d** from **600b** to afford 72 mg of **684** as a white solid, ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.25(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.3(s, 1H), 3.7(s, 3H), 4.25(m, 1H), 4.45-4.6(m, 3H), 7.4(br. s, 2H), 7.55(br. d, 4H).



10 (3*S*)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-

- 700 -

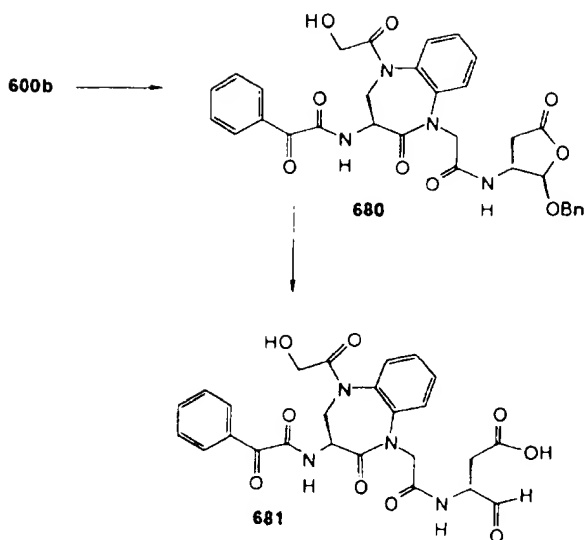
4.85(br. s, 2H), 7.3(br. m, 2H), 7.4-7.7(m, 5H),
8.15(d, 2H).



(3S)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-N-
[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide
(682), was synthesized from 600b by the methods used to
prepare 655 from 600b to afford 495 mg of 682 as a
white solid, ^1H NMR (CDCl_3) δ 2.00(s, 3H), 2.05(s, 3H),
2.47(d, 1H), 2.58(dd, 1H), 2.85(dd, 1H), 2.89(dd, 1H),
3.9(m, 2H), 4.05-4.15(m, 2H), 4.19(dd, 1H), 4.45(m,
2H), 4.55-5.05(m, 8H), 5.55(d, 1H), 6.85(d, 1H),
7.15(d, 1H), 7.25-7.55(m, 10H), 7.75(d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-
acetylamino]4-oxo-butanoic acid (683), was synthesized
from 682 by the method used to prepare 2002 from 2001
to afford 82 mg of 683 as a white solid, ^1H NMR (CD_3OD)
 δ 2.1(s, 3H), 2.5(m, 1H), 2.68(m, 1H), 3.8(m, 1H),
4.29(dd, 1H), 4.31(m, 1H), 4.45(d, 1H), 4.55(d, 1H),
4.6(d, 1H), 4.72(d, 1H), 4.95(br. s, 2H), 7.45(br. m,
2H), 7.52-7.65(br. m, 5H), 7.88(d, 2H).

- 699 -



(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-N-(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (680), was synthesized from 600b by the methods used to prepare

5 677 from 600b to afford 140 mg of 680 as a white solid, ^1H NMR (CDCl_3) δ 2.31(d, 1H), 2.4(dd, 2H), 2.75(dd, 2H), 2.85(dd, 1H), 3.36(br. s, 1H), 3.45(br. s, 1H), 3.6(br. t, 2H), 3.82(br. m, 2H), 3.95(br. d, 2H), 4.35(m, 2H), 4.42(d, 1H), 4.55(m, 1H), 4.70(d, 1H), 4.82(br. s, 2H),

10 5.5(d, 1H), 6.91(d, 1H), 7.25(br. m, 5H), 7.35-7.46(br. m, 3H), 7.5-7.6(m, 2H), 8.15(br. d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (681),

15 was synthesized from 680 by the method used to prepare 678 from 677 to afford 45 mg of 681 as a grey solid, ^1H NMR (CD_3OD) δ 2.5(m, 1H), 2.7(dt, 1H), 3.65-3.85(br. m, 3H), 4.05(m, 1H), 4.3(m, 1H), 4.5-4.7(br. m, 3H),

- 698 -

(3S)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (676), was synthesized from
5 675 by the method used to prepare 213e to afford 166 mg of 676 as a white solid.

(3S)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-
10 benzodiazepine-1-acetamide (677). A solution of TBAF (6 mL, 3 mmol) in HOAc (0.46 mL, 8 mmol) was added to 676 (0.213 g, 0.256 mmol). After 16 hours the reaction mixture was poured into EtOAc and washed twice with NaHCO₃, once with brine then dried over MgSO₄ and
15 concentrated *in vacuo* to afford 139 mg of 677 as a solid, ¹H NMR (CDCl₃) δ 2.4(d, 1H), 2.5(dd, 1H), 2.8(dd, 1H), 2.92(dd, 1H), 3.15(m, 2H), 3.55-3.65(m, 2H), 3.72(s, 6H), 3.92(m, 1H), 4.05(m, 1H), 4.3(m, 1H), 4.42(d, 1H), 4.6(dd, 1H), 4.65-4.8(m, 2H), 4.88(d, 1H),
20 5.55(d, 1H), 6.55(m, 2H), 6.75(d, 1H), 7.25-7.55(m, 8H), 7.75(m, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid (678),
25 was synthesized by the method used to prepare 667 from 666 to afford 54 mg of 678 as a white solid, ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.5(m, 2H), 3.75(br. s, 6H), 4.05(d, 1H), 4.3(m, 1H), 4.51-4.6(m, 2H), 4.8(br. m, 2H), 6.7(d, 2H), 7.4-7.5(br. m, 3H), 7.6-
30 7.65(br. m, 2H).

- 697 -

(3S)-2-Oxo-3-tert-butoxycarbonylamino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (672), was synthesized from 600b by method 1 used to prepare 602n
5 from 600b using 665 to afford 1.08 g of 672.

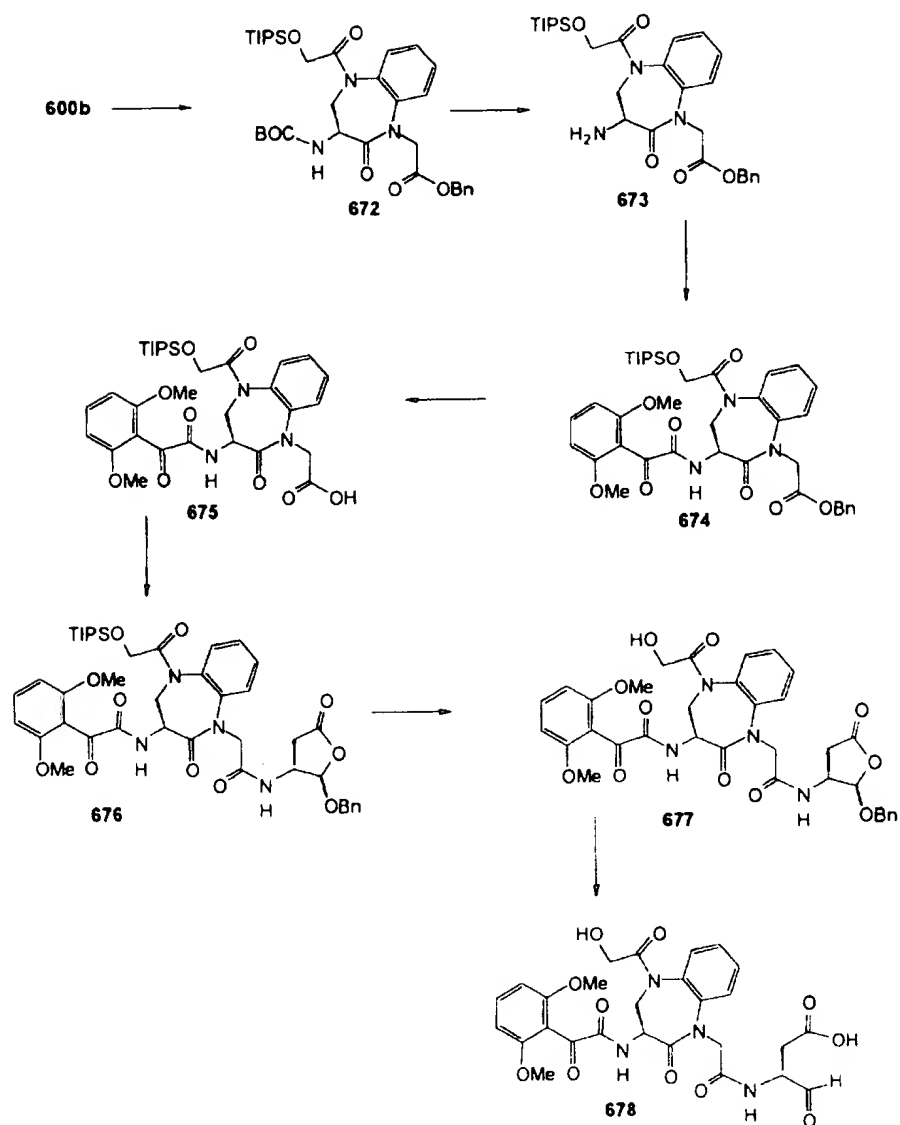
(3S)-2-Oxo-3-amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (673). To a solution of 672 (1.08 g, 1.69 mmol) in CH₂Cl₂ was added 2,6-lutidine (0.8 mL) then
10 TMSOTf (1 mL, 5.1 mmol). After 1 hour, the reaction mixture was poured into NaHCO₃ and extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo* to a small volume that was used directly for the next reaction.

15 (3S)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (674), was synthesized from 673 by the method used to prepare 602b to afford 0.91 g of 674.

20 (3S)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (675). A solution of 674 (0.365 g, 0.5 mmol) in MeOH was stirred with 1N NaOH (1.2 mL, 1.2 mmol). After 16 hours the reaction
25 mixture was concentrated *in vacuo* then dissolved in water and washed twice with ether. The aqueous layer was acidified with 1N HCl and the product extracted with EtOAc, dried over MgSO₄ and concentrated *in vacuo* to afford 337 mg of 675 as a solid.

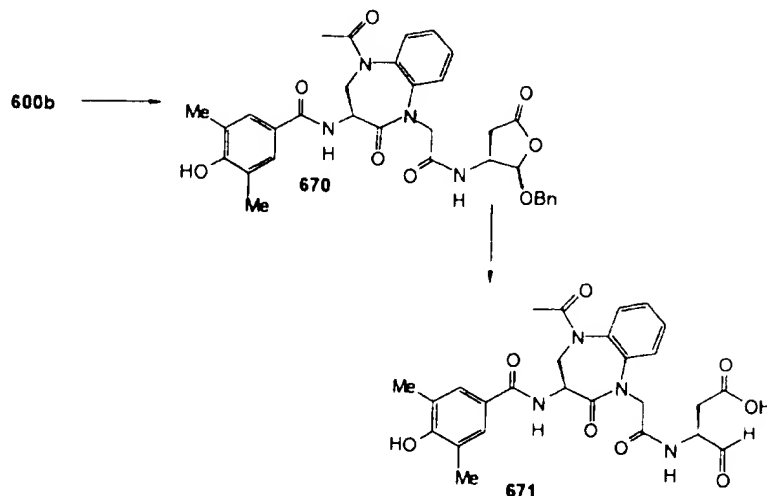
- 696 -

2.4-2.5 (m, 1H), 2.6-2.75 (m, 1H), 3.65-3.75 (m, 2H), 4.2-4.3 (m, 2H), 4.45-4.6 (m, 3H), 7.35-7.6 (m, 4H), 7.5 (s, 2H).



- 695 -

white solid, ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.4-2.7(m, 2H), 3.6-3.7(m, 2H), 3.9(s, 3H), 4.2-4.4(m, 2H), 4.4-4.6(m, 3H), 7.4-7.8(m, 4H), 7.9(s, 2H).



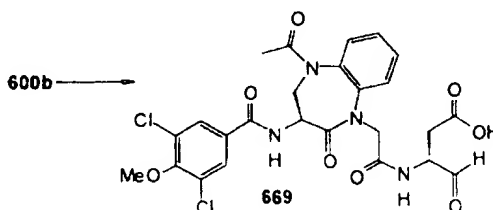
(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (670), was synthesized from 600b by the methods used to prepare 655 from 600b to afford 218 mg of 670 as a white solid, ^1H NMR (CD_3OD) δ 1.7, 1.75(2s, 3H), 2.15, 2.2(2s, 6H), 2.4-2.5(m, 1H), 2.6-2.75(m, 1H), 3.65-3.75(m, 2H), 4.2-4.3(m, 2H), 4.45-4.6(m, 3H), 7.35-7.6(m, 4H), 7.5(s, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid (671), was synthesized from 670 by the methods used to prepare 2002 from 2001 to afford 253 mg of 671 as a white solid, ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.25(s, 6H),

- 694 -

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid tert-butyl ester semicarbazone (**667**). To a solution of **666** (131 mg, 0.17 mmol) in tetrahydrofuran, cooled via ice-water bath, was added tetrabutylammonium fluoride (1M, 0.190 mL). After 2 hours the reaction mixture was poured into water, extracted twice with EtOAc, dried over MgSO₄ and concentrated *in vacuo* to afford 63 mg of **667** as a white solid.

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (**668**), was synthesized from **667** by the methods used to prepare **605d** from **604d** to afford 48 mg of **668** as a white solid, ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.67(dddd, 1H), 3.78(d, 1H), 3.85(br. m, 1H), 4.05(d, 1H), 4.28(m, 1H), 4.5(m, 2H), 4.65(m, 1H), 4.95(br. s, 2H), 7.4-7.5(m, 4H), 7.52-7.65(m, 3H), 7.88(d, 2H).



(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (**669**), was synthesized from **600b** by the methods used to prepare **605d** from **600b** to afford 63 mg of **669** as a

- 693 -

2-(Triisopropylsilyloxy)acetic acid benzyl ester (663).

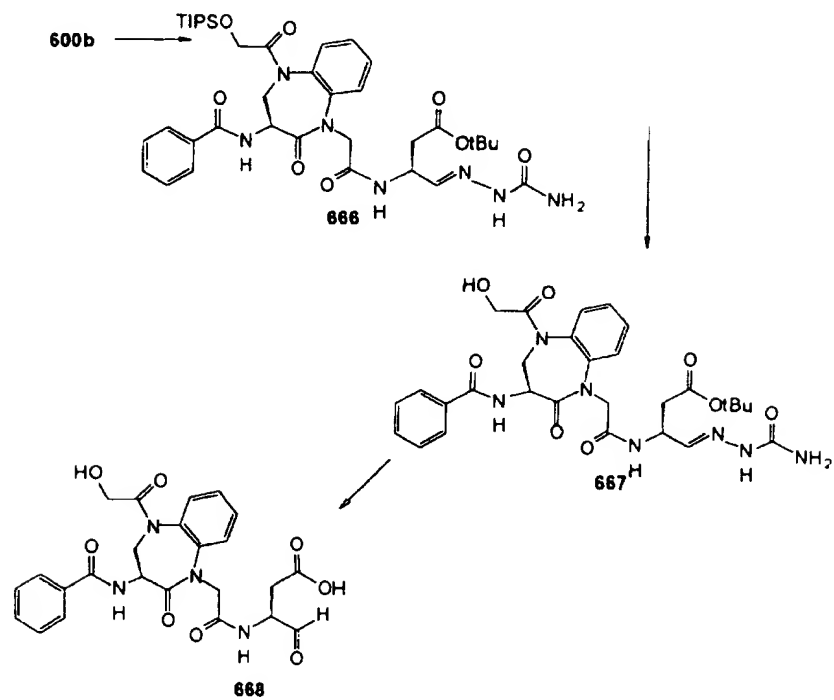
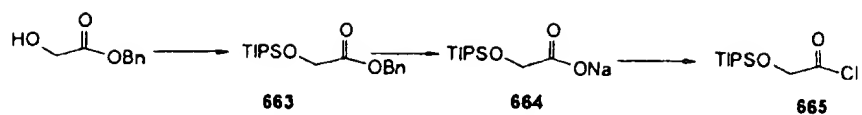
To a solution of benzyl glycolate (46.91g, 0.282 mol) and diisopropylethylamine (74 mLs, 0.423 mol) in CH_2Cl_2 , cooled via water bath, was added a solution of
5 TIPSOTf (95 g, 0.31 mol) in CH_2Cl_2 . The resulting mixture was allowed to warm to ambient temperature then poured into water, washed twice with 10% aqueous NaHSO_4 , dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (SiO_2 , 0 to 5% EtOAc in hexanes)
10 afforded 71.6 g of **663**.

2-(Triisopropylsilyloxy)acetic acid (664).

To a solution of **663** (0.4 g, 1.2 mmol) in EtOAc was added 10% Pd/C (33 mg). The resulting suspension was stirred under hydrogen atmosphere. After 15 hours, the
15 reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to afford 0.29 g of an oil. To a solution of this oil in 1,4-dioxane was added NaHCO_3 (0.5M, 2.4 mLs). The resulting solution was concentrated *in vacuo* from toluene to afford **664** as
20 a waxy solid.

2-(Triisopropylsilyloxy)acetyl chloride (665), was synthesized from **664** by a method similar that used to prepare **643** to afford **665** as a crude product.

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid tert-butyl ester semicarbazone (666), was synthesized from **600b**, using **665**, by methods used to prepare **604d** from **600b** to afford 131 mg of **666**.
25



- 691 -

from 600b, using 659, by methods used to prepare 604d from 600b to afford 453 mg of 660.

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrlic acid tert-butyl ester semicarbazone (661). A solution of 660 (423 mg) in MeOH:Et₂NH (1:1, v/v) was stirred at ambient temperature. After 10 minutes, the reaction mixture was concentrated *in vacuo* to a small volume. Precipitation by the addition of ether afforded 230 mg of 661.

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrlic acid (662), was synthesized from 661 by the methods used to prepare 605d from 604 to afford 37 mg of 662 as a white solid, ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.75(m, 1H), 3.9(d, 1H), 4.15(d, 1H), 4.35(m, 1H), 4.5(t, 2H), 4.7(dd, 1H), 7.4-7.6(m, 4H), 7.85(s, 2H).

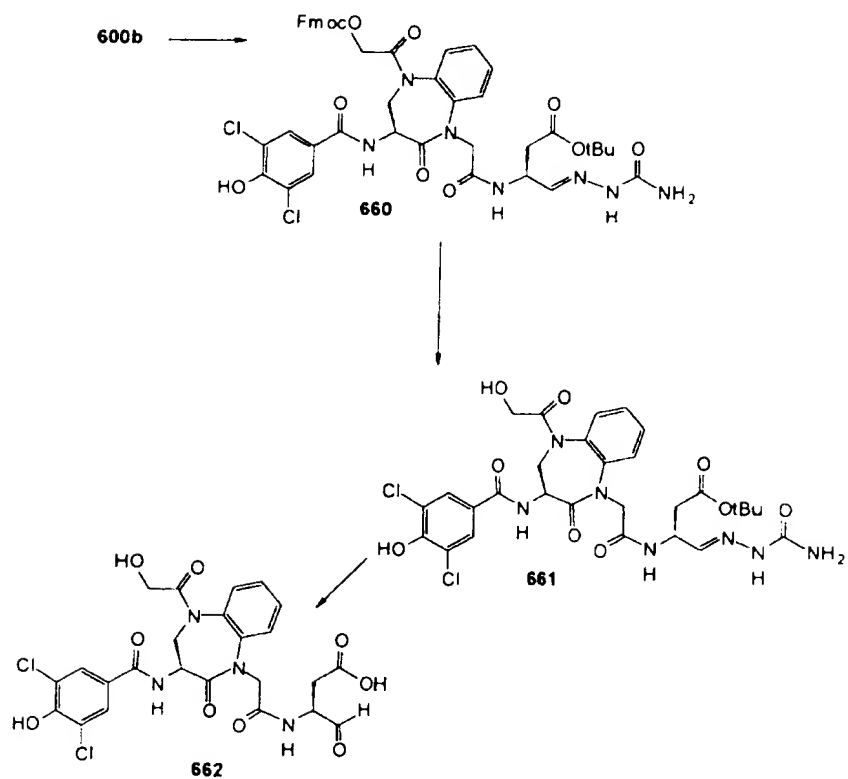
- 690 -

2-(Fluorenylmethoxycarbonyl)hydroxyacetic acid benzyl ester (657). To a solution of benzyl glycolate (6.0 g, 36.1 mmol) in CH₂Cl₂, cooled via ice-water bath, was added fluorenylmethoxy chloroformate (14 g, 1.5 equiv.) then diisopropylethylamine (9 mLs, 1.5 equiv.). After 1 hour, reaction mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with CH₂Cl₂, dried over Na₂SO₄ then concentrated in vacuo. The product was triturated from MeOH to obtain 2.2 g of 657 as a first crop of white solid.

2-(Fluorenylmethoxycarbonate) acetic acid (658). To a solution of 657 (2.2 g, 5.93 mmol) in tetrahydrofuran was added 5% Pd/C (220 mg). The resulting suspension was vigorously stirred under hydrogen atmosphere. After 90 min, the reaction mixture was filtered through Celite. The filtrate was poured into saturated aqueous NaHCO₃ and washed twice with EtOAc. The aqueous layer was then acidified and the product extracted twice with CH₂Cl₂, dried over Na₂SO₄ and concentrated in vacuo to afford 1.46 g (88%) of 658 as a white solid.

2-(Fluorenylmethoxycarbonate) acetyl chloride (659), was prepared from 658 by the method used to prepare 643 to afford 659 as a crude product.

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-fluorenylmethoxycarbonate)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrlic acid tert-butyl ester semicarbazone (660), was synthesized

$$\text{HO}-\text{CH}_2-\text{C}(=\text{O})-\text{OBn} \xrightarrow{\text{Fmoc-Cl}} \text{FmocO}-\text{CH}_2-\text{C}(=\text{O})-\text{OBn} \quad \text{657} \xrightarrow{\text{NaOH}} \text{FmocO}-\text{CH}_2-\text{C}(=\text{O})-\text{OH} \quad \text{658} \xrightarrow{\text{SOCl}_2} \text{FmocO}-\text{CH}_2-\text{C}(=\text{O})-\text{Cl} \quad \text{659}$$


- 688 -

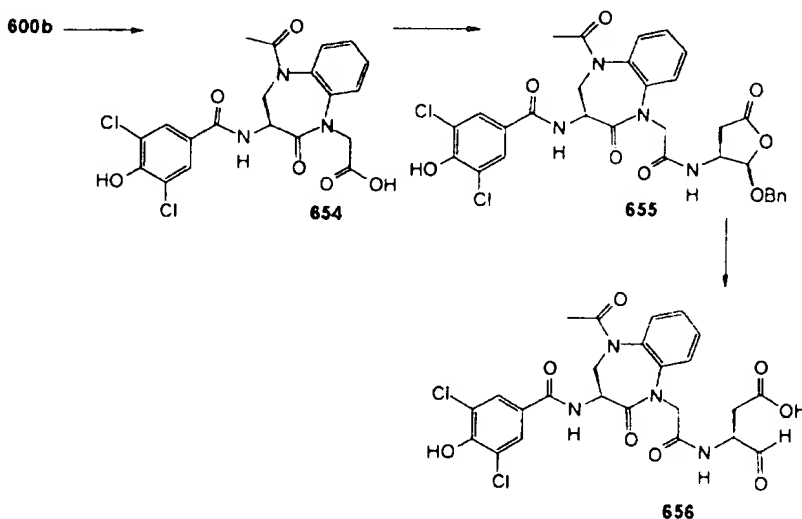
(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-acetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (655), was synthesized from 654 using the
5 method used to prepare 213e to afford 304 mg of 655, ¹H NMR (CD₃OD) δ 2.4(d, 1H), 2.6-2.75(m, 2H), 3.0(m, 1H), 3.45(m, 1H), 3.8(d, 1H), 4.0(t, 2H), 4.4(m, 2H), 4.5-4.55(m, 2H), 7.2-7.45(m, 4H), 7.85(s, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro, 4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (656), was synthesized from 655 using a method similar to that used to prepare 2002 from 2001 to afford 136 mg of 656 as a white solid, ¹H NMR (CD₃OD) δ 1.85(s, 3H),
10 2.5(m, 1H), 2.65(m, 1H), 3.7(m, 1H), 4.3(m, 1H),
15 4.55(m, 2H), 7.4-7.6(m, 4H), 7.85(s, 2H).

- 687 -

reagent obtained from reacting DMF with 3 equiv. of oxalyl chloride in a CH_2Cl_2 solution as R^3X , to afford 404 mg of 652.

(3S)-3-[(3S)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-
 5 2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-
 acetylamino]4-oxo-butyric acid (653), was synthesized
 from 652 by methods used to prepare 605d from 602d to
 afford 84 mg of 653 as a white solid, ^1H NMR (CD_3OD) δ
 2.3(m, 1H), 2.55(dd, 1H), 3.75(br. s, 1H), 4.25-4.6(m
 10 5H), 5.15(m, 1H), 7.2-7.45(m, 6H), 7.8-7.9(dd, 3H),
 8.1(s, 1H), 8.2(m, 2H).



(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-
 acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-
 acetic acid (654), was synthesized from 600b using
 15 methods similar to those used for preparing 603d from
 600b to afford 775 mg of 654.

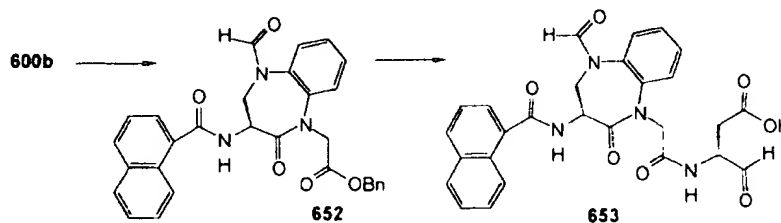
- 686 -

synthesized from **647** by methods used to prepare **604d** from **602d** to afford 409 mg of **648**.

(3S)-3-[(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methylamino) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid tert-butyl ester semicarbazone (649).

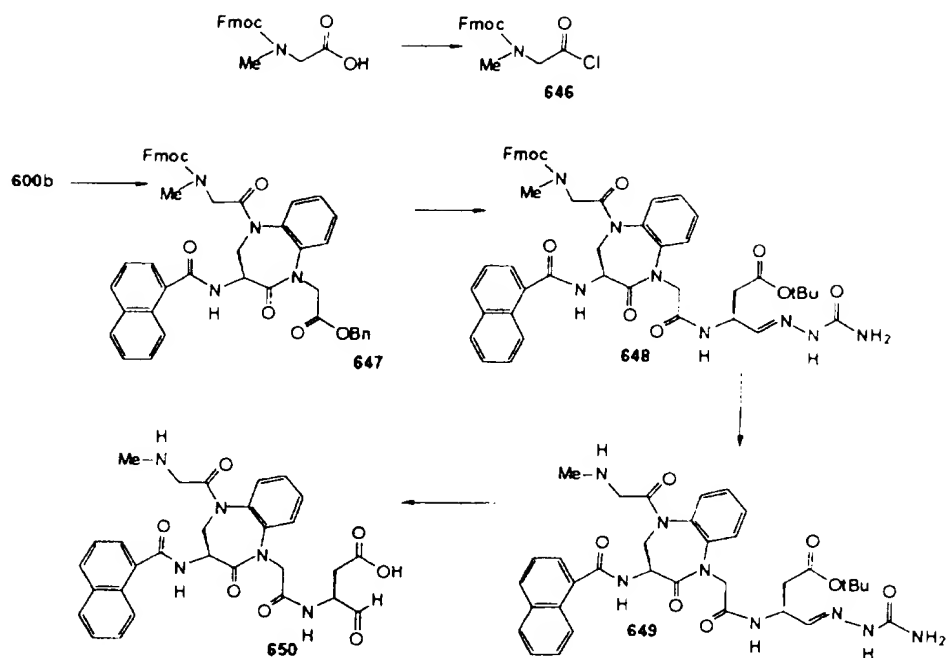
A solution of **648** (409 mg, 0.465 mmol) in MeCN:Et₂NH (4:1, v/v) was stirred at ambient temperature. After 45 minutes, the reaction mixture was concentrated in vacuo. Flash chromatography (SiO₂, 5% to 20% MeOH in CH₂Cl₂) afforded 241 mg of **649**.

(3S)-3-[(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methylamino) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (650), was synthesized from **649** by methods used to prepare **605d** from **604** to afford 179 mg of **650** as a white solid, ¹H NMR (CD₃OD) δ 2.4-2.6(m, 2H), 2.7(s, 3H), 3.5(q, 1H), 3.8(m, 2H), 4.2-4.4(m, 2H), 4.3-4.45(m, 1H), 5.0-5.1(m, 2H), 7.4-7.7(m, 6H), 7.85-7.9(m, 2H), 8.2(m, 1H).



(3S)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (652), was synthesized from **600b** by methods similar to those used to make **602n** from **600b**, using the

- 685 -



2-(*N*-Methyl, *N*-fluorenylmethoxycarbonyl)aminoacetyl chloride (646), was prepared from *N*-Fmoc-sarcosine by method used to make 643 to afford 646 as a crude product.

- 5 (3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl)amino]acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (647), was synthesized from 600b by methods used to synthesize 602d from 600b, using 646 to afford 481
- 10 mg of 647.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl)amino]acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butylric acid *tert*-butyl ester semicarbazone (648), was

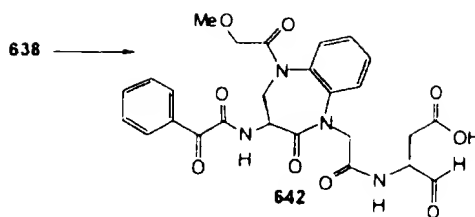
- 684 -

(0.450 mLs, 5.1 mmol). After stirring 30 minutes at ambient temperature, the mixture was concentrated to afford 643 as a crude product.

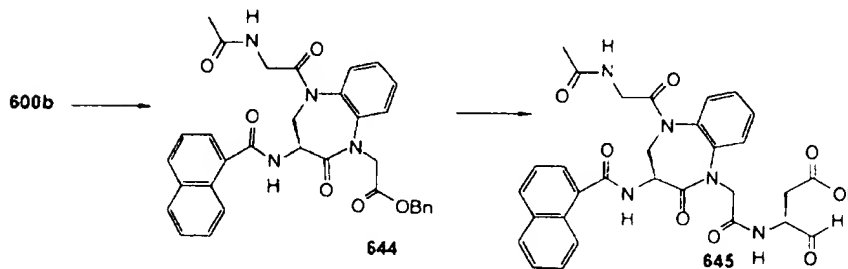
(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-acetamido)acetyl-
5 2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid
benzyl ester (644), was synthesized from 600b by
methods used to make 602d from 600b using 643 to afford
112 mg of 644.

(3S)-3-[(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-
10 acetamido)acetyl-2,3,4,5-tetrahydro-1H-1,5-
benzodiazepine-1-acetylamino]4-oxo-butyric acid (645),
was synthesized from 644 by methods used to make 605d
from 602d to afford 43 mg of 645 as a white solid, ¹H
NMR (CD₃OD) δ 1.95(s, 3H), 2.4(m, 1H), 2.65(m, 1H),
15 3.4(s, 1H), 3.55(m, 1H), 3.85(m, 1H), 4.05(d, 1H),
4.3(m, 1H), 4.4-4.6(m, 2H), 5.0(m, 1H), 7.4-7.7(m, 6H),
7.85-8.0(m, 2H).

- 683 -



(3S)-3-[(3S)-2-Oxo-3-benzoylformylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid (642), was synthesized from 638 by similar methods used to make 605m to afford
 5 213 mg of 642, ^1H NMR (CD_3OD) δ 2.5(m, 1H), 2.68(ddd, 1H), 3.25(s, 2H), 3.3(s, 3H), 3.78(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.6(m, 2H), 4.85(br. s, 2H), 7.08-7.22(m, 2H), 7.35(m, 1H), 7.4-7.65(m, 4H), 7.7(dd, 1H), 8.1(ddd, 1H).



10 2-Acetamido-acetyl chloride (643). To a suspension of N-acetyl glycine (200 mg, 1.7 mmol) in CH_2Cl_2 (2.5 mLs) containing DMF (0.005 mLs) was added oxalyl chloride

- 682 -

(3S)-2-Oxo-3-amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (638), was synthesized from 600a by methods similar to those used for making 602m from 600a to afford 2.4g of 638 as a white solid.

(3S)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (639). To a solution of 638 (630 mg, 1.76 mmol) and 2-naphthylmethyl bromide (428 mg, 1.94 mmol) in CH₃CN was added K₂CO₃ (608 mg, 4.4 mmol). The resulting mixture was stirred at ambient temperature. After 18 hours, the reaction mixture was diluted with CH₂Cl₂, washed with water then brine, dried over Na₂SO₄ then concentrated in vacuo. Flash chromatography (SiO₂, 0 to 20% EtOAc/CH₂Cl₂) afforded 450mg of 639.

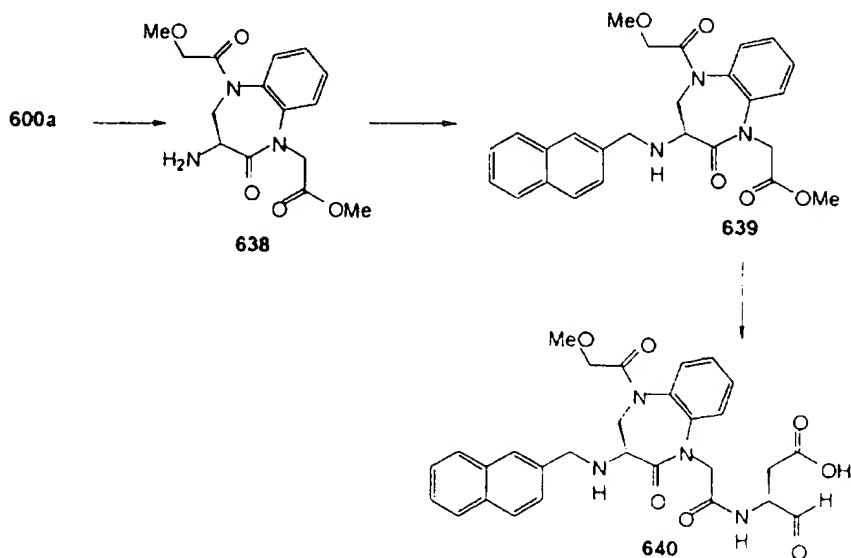
(3S)-3-[(3S)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (640), was synthesized by methods used to make 605v from 602v to afford 205 mg of 640 as a white solid, ¹H NMR (CDCl₃) δ 2.4-2.55(m, 1H), 2.65-2.8(m, 1H), 3.2(s, 3H), 3.72-3.78(m, 1H), 3.85-4.0(m, 2H), 4.22-4.28(d, 1H), 4.26-4.5(m, 4H), 4.58-4.75(m, 1H), 4.78-4.85(m, 1H), 5.0-5.08(t, 1H), 7.35-7.65(m, 7H), 7.85-8.02(m, 4H).

- 681 -

58 $\frac{1}{2}$): mp. 124-32°C; IR (KBr) 3312, 2979, 1790, 1664, 1610, 1532, 1485, 1285, 1120, 1037, 932; ^1H NMR (D_6 -DMSO) δ 10.39 (1H, s), 8.71 (0.5H, d), 8.43 (0.5H, d), 7.45 (1H, d), 7.36 (1H, s), 7.04 (1H, d), 6.12 (2H, s), 5.58 (0.5H, d), 5.34 (0.5H, s), 4.95-4.85 (1H, m), 4.70-4.52 (0.5H, m), 4.35-4.10 (1.5H, m), 3.95-3.50 (5H, m), 3.03 (0.5H, dd), 2.90-2.55 (1.5H, m), 2.46-2.20 (2H, m), 2.10-2.40 (4H, m), 1.16-1.13 (3H, 2 x t). Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_9 \cdot 0.6\text{H}_2\text{O}$: C, 52.29; H, 5.38; N, 13.26. Found: C, 52.53; H, 5.35; N, 12.78. MS (ES^+) 519 ($\text{M}^+ + 2$, 27%), 518 ($\text{M}^+ + 1$, 100), 472 (7), 374 (12), 373 (53), 345 (14), 149 (12).

Example 31

Compounds 640, 642, 645, 650, 653, 655, 656, 662, 668, 669, 670, 671, 677, 678, 681, 682, 683, 684, 686, 688a, 688b, 6891, 689b, 690a, 690b, 691a, 691b, 695a, 695b, 695c, 692a, 692b, 693 and 694 were prepared as follows.

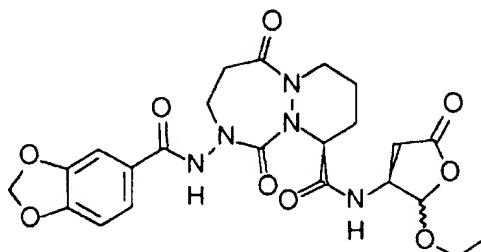


- 680 -

$C_{27}H_{34}N_8O_7S$: C, 52.76; H, 5.58; N, 18.23. Found: C, 52.25; H, 5.74; N, 16.30. MS (ES^+) 615.

[3*S*(4*S*)] 3-[7-(Benzo[*b*]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-

- 5 pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1053), was prepared by a similar method as used for 214 to afford a white solid (106mg, 73%): $[\alpha]_D^{20} +22^\circ$ (c 0.10, MeOH); IR (KBr) 3428, 2944, 1733, 1652, 1532, 1433, 1337, 1288, 1186; 1H NMR
- 10 (CD₃OD) δ 7.95 (1*H*, s), 7.90-7.85 (2*H*, m), 7.43-7.35 (2*H*, m), 4.98 (1*H*, m), 4.65-4.52 (1*H*, m), 4.40-4.20 (2*H*, m), 3.85-3.70 (3*H*, m), 3.30-3.25 (3*H*, m), 3.03-2.85 (1*H*, m), 2.70-2.31 (3*H*, m), 2.10-1.55 (4*H*, m). MS (ES^+) 500 (as methyl acetal of the aldehyde).



15

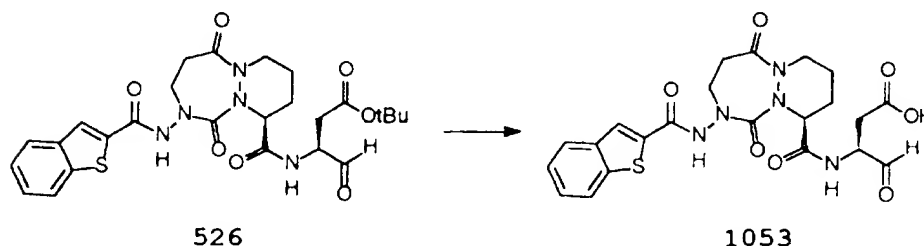
528

[4*S*(2*RS*,3*S*)] 6,10-Dioxo-*N*-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamide

- 20 (528), was prepared by a similar method as compound 213*e* to afford a mixture of diastereomers (Syn: anti isomer ratio 1:1) as a creamy white foamy solid (1.05g,

- 679 -

[3S(4S)] 3-[6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1015), was prepared by a similar method as used for 265 to afford a white solid (142mg, 58%): mp. 170-5°C; $[\alpha]_D^{25} +32.7^\circ$ (c 0.1, CH₃OH); IR (KBr) 3700-2500 (br), 3325, 2969, 1784, 1662, 1485, 1440, 1292, 1258, 1037; ¹H NMR (CD₃OD) δ 7.45 (1H, dd), 7.32 (1H, d), 6.90 (1H, d), 6.05 (2H, s), 5.10-4.90 (1H, m), 4.62-4.54 (1H, m), 4.45-4.35 (1H, m), 4.33-4.22 (1H, m), 3.95-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.20-1.50 (4H, m).



[3S(4S)] t-Butyl 3-[7-(benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine]-4-oxobutanoate semicarbazone (526), was prepared by a similar method as used for 502 to afford a glassy solid: $[\alpha]_D^{20} +34^\circ$ (c 0.13, CH₂Cl₂); IR (KBr) 3437, 2929, 1670, 1530, 1428, 1288, 1156; ¹H NMR (CDCl₃) δ 10.0 (1H, bs), 9.74 (1H, bs), 7.93 (1H, s), 7.80-7.60 (2H, m), 7.40-7.18 (3H, m), 6.15-5.30 (2H, bs), 5.00-4.85 (2H, m), 4.50-4.25 (1H, m), 3.95-3.75 (3H, m), 3.12-2.78 (2H, m), 2.73-1.60 (7H, m), 1.36 (9H, s). Anal. Calcd for

- 678 -

(0.194g, 100%): mp. 138-142°C; $[\alpha]_D^{20} +36.3^\circ$ (c 0.19, CH₃OH); IR (KBr) 3434-2962, 1782, 1660, 1607, 1537, 1504, 1441, 1424, 1313, 1293, 1258, 1177; ¹H NMR (CD₃OD) δ 7.11 (2H, d, J = 8.8), 6.90 (2H, d, J = 8.9),
5 4.48 (1H, m), 4.34, 4.28 (1H, 2m), 4.15 (1H, m), 3.75 (3H, s), 3.75, 3.70 (3H, m), 2.88, 2.49, 2.28, 2.23, 2.00, 1.86, 1.79, 1.58 (8H, m).

[3S(4S)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1027), was synthesized by a similar method as compound 265 to afford a white foam (88%):
 $[\alpha]_D^{24} +22.6^\circ$ (c 0.17, MeOH); IR (KBr) 3349, 1789, 1663, 1537, 1448, 1337, 1169, 1092, 690; ¹H NMR (CD₃OD)
15 δ 7.82 (2H, d, J = 7.8), 7.57 (3H, m), 4.74 (1H, m), 4.47 (1H, m), 4.24-4.10 (2H, m), 3.72-3.47 (4H, m), 2.62-2.48 (3H, m), 2.20 (1H, m), 1.94-1.35 (3H, m). MS (ES⁺) 480 (M⁺ - 1, 100%). Accurate mass calculated for C₁₉H₂₄SN₅O₈ (MH⁺): 482.1346. Found: 482.1325.

20 [3S(4S)] 3-[6,10-Dioxo-7-(4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1056), was prepared by the method used for 265 (95%): mp. >300°C; IR (KBr) 3392, 1660,
25 1610, 1507, 1442, 1280, 1171, 1149, 1133. ¹H NMR (CD₃OD) δ 7.74 (2H, d J = 8.7), 6.84 (2H, d J = 8.7) 4.58 (1H, m), 4.41 (1H, bd, J = 12.6), 4.28 (1H, m), 3.85 (3H, m), 2.98 (1H, m), 2.8-2.3 (3H, m), 2.3-1.6 (4H, m).

- 677 -

oxobutanoic acid (1075), was prepared by a similar method as compound 265 to afford a white solid (184mg, 83%): mp. 210-5°C; $[\alpha]_D^{24} +43.9^\circ$ (c 0.1, CH₃OH); IR (KBr) 3700-2300 (br), 3309, 1660, 1537, 1423, 1311, 1262, 1184; ¹H NMR (CD₃OD) δ 7.61 (1H, d), 7.45 (1H, d), 7.28-7.15 (1H, m), 7.15-7.00 (1H, m), 7.13 (1H, s), 5.12-4.96 (1H, m), 4.62-4.55 (1H, m), 4.50-4.25 (2H, m), 4.00-3.69 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.25-1.50 (4H, m). MS (ES⁺) 484 (M⁺, 26%), 483 (M⁺ - 1, 100), 383 (25), 245 (12), 208 (11), 200 (21), 174 (31), 137 (18).

[3S(4S)] 3-{7-[(4-Acetamido)benzamido]-6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxamido}-4-oxobutanoic acid (1018), was prepared by a similar method as compound 265 to afford a white solid (177mg, 82%): mp. 235-40°C; $[\alpha]_D^{23} +27.3^\circ$ (c 0.1, CH₃OH); IR (KBr) 3700-2300 (br), 3311, 2957, 1662, 1599, 1531, 1318, 1266, 1182; ¹H NMR (CD₃OD) δ 7.83 (2H, d), 7.69 (2H, d), 5.10-4.95 (1H, m), 4.64-4.55 (1H, m), 4.50-4.35 (1H, m), 4.32-4.22 (1H, m), 4.00-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.15 (3H, s), 2.15-1.50 (4H, m). Anal. Calcd for C₂₂H₂₆N₆O₈•1.5H₂O: C, 49.90; H, 5.52; N, 15.87. Found: C, 50.21; H, 5.41; N, 15.49. MS (ES⁺) 502 (M⁺, 28%), 501 (M⁺ - 1, 100), 401 (8), 218 (4), 119 (2), 118 (5), 113 (16).

[3S(4S)] 3-[6,10-Dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1052), was synthesized via method used to prepare 265 to afford a white solid

- 676 -

[3S(4S)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetyl-amino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1095), was prepared by a similar method as compound 265 to afford a white solid (84mg, 90%): mp. 180-6°C; $[\alpha]_D^{22} +22.3^\circ$ (c 0.065, CH₃OH); IR (KBr) 3700-2300 (br), 3287, 1664, 1536, 1425, 1261, 1181; ¹H NMR (CD₃OD) δ 7.35-7.20 (5H, m), 5.00-4.90 (1H, m), 4.60-4.50 (1H, m), 4.50-4.10 (2H, m), 3.90-3.50 (3H, m), 3.54 (2H, s), 3.00-2.80 (1H, m), 2.80-2.40 (2H, m), 2.35-2.20 (1H, m), 2.20-1.50 (4H, m). MS (ES⁺) 459 (M⁺ 24%), 458 (M⁺ - 1, 100), 358 (27), 175 (9), 149 (7), 137 (12). Accurate mass calculated for C₂₁H₂₆N₅O₇ (MH⁺): 460.1832. found: 460.1840.

15 [3S(4S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265f), was prepared by a similar method as compound 265 to afford a white foamy solid (130mg, 88%): mp. 157-62°C; $[\alpha]_D^{24} +41.7^\circ$ (c 0.1, CH₃OH); IR (KBr) 3700-2300 (br), 3325, 1782, 1663, 1547, 1443, 1315, 1242, 1181; ¹H NMR (CD₃OD) δ 7.40 (2H, dd), 7.35-7.20 (2H, m), 7.06-6.95 (1H, m), 5.05-4.95 (1H, m), 4.64-4.54 (1H, m), 4.50-4.35 (1H, m), 4.35-4.15 (1H, m), 3.90-3.69 (3H, m), 3.00-2.85 (1H, m), 2.80-2.45 (3H, m), 3.40-1.50 (4H, m). MS (ES⁺) 460 (M⁺, 24%), 459 (M⁺ - 1, 100), 341 (9), 340 (54), 296 (6), 239 (9).

[3S(4S)] 3-[6,10-Dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-

- 675 -

17%): mp. 126-30°C (dec); $[\alpha]_D^{20} +30^\circ$ (c 0.05, MeOH);
IR (KBr) 3371, 2935, 1785, 1663, 1538, 1418, 1339,
1164, 669; ^1H NMR (CD_3OD) δ 8.44 (1H, s), 8.06-7.50 (7H,
m), 7.22 (1H, d, $J = 8.4$), 4.58-4.57 (1H, m), 4.46-4.42
5 (1H, m), 4.16-4.09 (2H, m), 3.85-3.50 (3H, m), 2.84-
2.78 (1H, m), 2.64-2.51 (1H, m), 2.44-2.15 (2H, m),
1.81-0.89 (4H, m). Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}_8\text{S}\cdot\text{H}_2\text{O}$: C,
50.27; H, 4.95; N, 12.74. Found: C, 50.33; H, 5.04; N,
12.60. MS (ES^+) 530.

10 **[3S(4S)] 3-[6,10-Dioxo-7-(3-methoxyphenylureido)-
1,2,3,4,7,8,9,10-octahydro-6H-
pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-
oxobutanoic acid (265c)**, was prepared by a similar
method as 265, (90%) as a colourless solid: mp. ~150°C
15 (decomp.); $[\alpha]_D^{23} +94.8^\circ$ (c 0.1, 20% MeOH/ CH_2Cl_2); IR
(KBr) 3330, 1780, 1660, 1610, 1550, 1495, 1428, 1326,
1287, 1251, 1223, 1160; ^1H NMR (CD_3OD) δ 7.16 (2H, m),
6.89 (1H, d, $J = 7.8$), 4.58 (1H, m), 4.37 (2H, m), 3.76
(6H, s + m), 2.95 (1H, m), 2.67 (1H, m), 2.33 (1H, m),
20 2.20-1.85 (3H, m), 1.66 (1H, m).

**[3S(4S)] 3-[6,10-Dioxo-7-(2-methoxyphenylureido)-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-
triazepine-4-carboxamido]-4-oxobutanoic acid (265d)**,
was prepared by a similar method as 265, (85%) as a
25 colourless solid: mp. ~176-85°C; $[\alpha]_D^{23} +11.0^\circ$ (c 0.1,
MeOH); IR (KBr) 3392, 3328, 1784w, 1665, 1603, 1537,
1490, 1462, 1437, 1337, 1290, 1290, 1217, 1177, 1119,
1023; ^1H NMR (CD_3OD) δ 8.02 (2H, m), 6.95 (4H, m), 5.05
(1H, m), 4.60 (2H, m), 3.92 (4H, s + m), 3.00 (2H, m),
30 2.68 (1H, m), 2.39 (1H, m), 2.00 (4H, m), 1.69 (1H, m).

- 674 -

(264k), was prepared by the method used for 213e (96%):
IR (KBr) 3294, 2946, 1793, 1658, 1606, 1535, 1501,
1248, 1174, 1119. ¹H NMR (CDCl₃) δ 8.91 (1H, s), 7.85
(3H, m), 7.4 (10H, m), 7.02 (2H, d), 5.35 (1H, s), 5.10
5 (2H, s), 4.8-4.3 (5H, m), 4.00 (1H, bs), 3.78 (2H, m),
2.90 (2H, m), 2.5-1.5 (6H, m).

[4S(2RS,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-
6,10-dioxo-7-(3,4-methylenedioxybenzoylamino)-
1,2,3,4,7,8,9,10-octahydro-6H-
10 pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide
(2641), was prepared by a similar method as compound
213e to afford a mixture of diastereomers (syn:anti
isomer ratio 1:1) as a white solid (1.72g, 71%): mp.
148-60°C; IR (KBr) 3314, 1780, 1677, 1658, 1651, 1550,
15 1485, 1439, 1258, 1132, 1038, 943; ¹H NMR (D₆-DMSO) δ
10.39 (1H, s), 8.71 (0.5H, d), 8.49 (0.5H, d), 7.44
(1H, d), 7.42-7.30 (6H, m), 7.03 (1H, d), 6.12 (2H, s),
5.68 (0.5H, d), 5.45 (0.5H, s), 4.90-4.82 (1H, m),
4.82-4.58 (2.5H, m), 4.40-4.10 (1.5H, m), 3.90-3.65
20 (2H, m), 3.65-3.43 (1H, m), 3.09 (0.5H, dd), 2.90-2.55
(1.5H, m), 2.45-2.10 (2H, m), 2.10-1.35 (4H, m). Anal.
Calcd for C₂₈H₂₉N₅O₉•0.2H₂O: C, 57.67; H, 5.08; N,
12.01. Found: C, 58.01; H, 5.33; N, 11.51. MS (ES⁺)
581 (M⁺ + 2, 33%), 580 (M⁺, 100), 374 (9), 373 (48),
25 345 (12), 261 (4), 239 (7), 149 (9).

[3S(4S)] 3-[6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-
1,2,3,4,7,8,9,10-octahydro-6H-
pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-
oxobutanoic acid (265a), was prepared by a similar
30 method as compound 265 to afford a white solid (37mg,

- 673 -

(264i), was prepared by a similar method to that described for compound 213e to afford a white solid (70%): mp. 116-118°C; IR (KBr) 3315, 2951, 1793, 1664, 1607, 1502, 1258, 1177; ¹H NMR (CDCl₃) δ 8.07 (1H, s),
5 7.77 (2H, d, J = 8.6), 7.35 (5H, m), 6.94 (2H, d, J = 8.5), 6.74 (1H), 4.89 (1H, d, J = 11.1), 4.74 (1H, m), 4.60 (1H, d, J = 11.0), 4.48, 4.41 (1H, 2m), 3.86 (3H, s), 3.79, 3.71-3.53 (3H, 2m), 2.87 (2H, m), 2.44 (1H, m), 2.18, 1.91, 1.68 (5H, 3m).

10 [4S(2S,3S)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264j), was synthesized by a similar method as compound
15 213e to afford a foam (88%): [α]_D²⁴ +74.2° (c 0.36, CH₂Cl₂); IR (KBr) 3332, 3235, 1793, 1664, 1537, 1448, 1416, 1337, 1169, 118, 1092, 940, 690; ¹H NMR (CDCl₃) δ 7.99 (1H, s), 7.88 (2H, d, J = 6.8), 7.64-7.48 (3H, m), 7.34 (5H, s), 7.13 (1H, d, J = 6.9), 5.39 (1H, s), 4.81
20 (2H, m), 4.62 (1H, d, J = 11.5), 4.48 (1H, m), 4.33 (1H, m), 3.85 (1H, m), 3.59 (2H, m), 3.03 (1H, dd, J = 7.6, 18.2), 2.49-2.28 (3H, m), 1.94-1.40 (4H, m).
Anal. Calcd for C₂₆H₂₉SN₅O₈: C, 54.63; H, 5.11 N, 12.25. Found: C, 54.42; H, 5.28; N, 11.62. MS (ES⁺) 572 (MH⁺,
25 100%). Accurate mass calculated for C₂₆H₃₀SN₅O₈ (MH⁺): 572.1815. Found: 572.1802.

[4S(2RS,3S)] 7-(4-Benzoyloxyphenyl)carbonylamino-N-(2-benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide
30

- 672 -

CH₂Cl₂); IR (KBr) 3404, 3295, 1789, 1660, 1536, 1421, 1310, 1260, 1122, 749; ¹H NMR (D₆-DMSO) δ 11.72 (1H, s), 10.58 (1H, s), 8.73 (1H, d), 7.65 (1H, d), 7.58-7.27 (6H, m), 7.27-7.10 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m), 5.46 (1H, s), 4.90-4.85 (1H, m), 4.77 and 4.68 (2H, dd), 4.35-4.25 (2H, m), 3.95-3.55 (3H, m), 3.09 (1H, dd), 2.95-2.80 (1H, m), 2.47-2.25 (2H, m), 2.10-1.35 (4H, m). MS (ES⁺) 574 (M⁺, 35%), 573 (M⁺ - 1, 100), 384 (16), 383 (69), 341 (23), 327 (12), 267 (13), 200 (22).

[4*S*(2*RS*,3*S*)] 7-[(4-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamide (264h), was prepared by a similar method as compound 213e to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white solid (276mg, 70%): mp. 147-52°C; IR (KBr) 3444, 3304, 1793, 1665, 1602, 1531, 1505, 1423, 1294, 1264, 1181, 1123, 966; ¹H NMR (D₆-DMSO) δ 10.41 (1H, s), 10.22 (1H, s), 8.71 (0.1H, d), 8.48 (0.9H, d), 7.78 (2H, d), 7.67 (2H, d), 7.35-7.30 (5H, m), 5.68 (0.9H, d), 5.45 (0.1H, s), 4.88-4.80 (1H, m), 4.75-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.90-3.50 (3H, m), 3.10-2.50 (3H, m), 2.35-2.20 (1H, m), 2.07 (3H, s), 2.05-1.35 (4H, m). Anal. Calcd for C₂₉H₃₂N₆O₈·1H₂O: C, 57.04; H, 5.61; N, 13.76. Found: C, 56.79; H, 5.50; N, 13.53. MS (ES⁺) 594 (M⁺ + 2, 34%), 593 (M⁺ + 1, 100), 387 (8), 386 (38), 358 (8), 162 (19).

[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamide

- 671 -

4.85-4.75 (1H, m), 4.74-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.10 (1H, m), 3.80-3.40 (3H, m), 3.43 (2H, s), 3.10-2.40 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for $C_{28}H_{31}N_5O_7 \cdot 0.5H_2O$: C, 60.21; H, 5.77; N, 12.53. Found: C, 60.38; H, 5.83; N, 12.13. MS (ES^+) 551 ($M^+ + 2$, 33%), 550 ($M^+ + 1$, 100), 480 (7), 343 (8), 279 (4).

[4S(2RS,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264f), was prepared by a similar method as compound 213e to afford the pure syn-isomer as a white foamy solid (225mg, 82%): mp. 130-5°C; $[\alpha]_D^{24} +10.8^\circ$ (c 0.1, CH_2Cl_2); IR (KBr) 3316, 1791, 1688, 1676, 1664, 1601, 1536, 1445, 1314, 1242, 973; 1H NMR (D_6 -DMSO) δ 8.84 (1H, s), 8.49 (1H, d), 8.19 (1H, s), 7.45-7.18 (9H, m), 7.00-6.90 (1H, m), 5.68 (1H, d), 4.90-4.81 (1H, m), 4.75-4.60 (1H, m), 4.78 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.75-3.55 (3H, m), 2.85-2.55 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for $C_{27}H_{30}N_6O_7 \cdot 0.5H_2O$: C, 57.95; H, 5.58; N, 15.02. Found: C, 58.12; H, 5.64; N, 14.81. MS (ES^+) 552 ($M^+ + 2$, 30%), 551 ($M^+ + 1$, 100), 362 (19), 299 (10), 279 (4).

[4S(2S,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264g), was prepared by a similar method as compound 213e to afford the pure anti-isomer as a white solid (284mg, 80%): mp. 148-53°C; $[\alpha]_D^{24} -72.0^\circ$ (c 0.1,

- 670 -

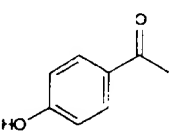
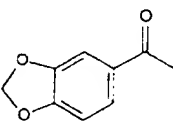
1608, 1543, 1496, 1455, 1428, 1325, 1287, 1250, 1218, 1160, 1118; ¹H NMR (CDCl₃) δ 8.00 (1H, d, J = 7.1), 7.66 (1H, s), 7.55 (1H, s), 7.28 (5H, m), 7.14 (2H, m), 6.87 (1H, d, J = 7.4), 6.59 (1H, m), 5.42 (1H, s), 4.66 (5H, m), 3.90-3.65 (4H, m), 3.73 (3H, s), 2.98 (2H, m), 2.38 (2H, m), 2.01-1.65 (3H, m).

[4S(2S,3S)] N-(2-Benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-1-carboxamide (264d), was prepared by a similar method as **213e**, (72%) as colourless foam: $[\alpha]_D^{22} +21.4^\circ$ (c 0.1, CH₂Cl₂); IR (KBr) 3302, 1791, 1689, 1678, 1664, 1602, 1536, 1489, 1461, 1437, 1420, 1249, 1119, 1023, 942, 751; ¹H NMR (CDCl₃) δ 8.07 (1H, d, J = 7.7), 7.82 (1H, s), 7.68 (1H, d, J = 6.7), 7.49 (1H, s), 7.34 (5H, m), 6.96 (3H, m), 5.47 (1H, s), 4.82 (2H, d + m, J = 11.5), 4.63 (1H, d, J = 11.5), 4.49 (2H, m), 3.85 (4H, s + m), 3.68 (2H, m), 3.01 (2H, m), 2.46 (2H, m), 1.95 (3H, m), 1.57 (1H, m).

[4S(2RS,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetyl-amino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264e) was synthesized via a similar method as used to prepare **213e** to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white glassy solid (128mg, 78%): mp. 103-8°C; IR (KBr) 3419, 3302, 1793, 1664, 1535, 1421, 1327, 1256, 1123, 973; ¹H NMR (D₆-DMSO) δ 10.20 (0.9H, s), 9.35 (0.1H, s), 8.74 (0.1H, d), 8.49 (0.9H, d), 7.36-7.15 (10H, m), 5.67 (0.9H, d), 5.44 (0.1H, s),

- 669 -

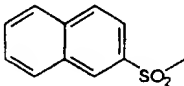
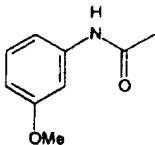
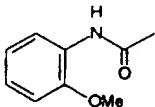
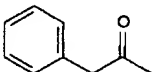
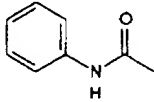
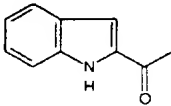
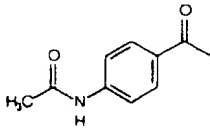
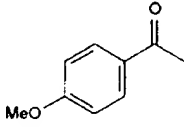
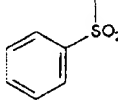
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264k 1056	
264l 1015	

25 [4*S*(2*S*,3*S*)] *N*-(2-Benzoyloxy-5-oxo-tetrahydrofuran-3-yl)-
6,10-dioxo-7-(2-naphthalenesulfonyl)amino-
1,2,3,4,7,8,9,10-octahydro-6*H*-
pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamide
(264a), was synthesized by a similar method as compound
213e to afford a white solid (240mg, 82%): IR (KBr)
30 3380, 3066, 2947, 1789, 1750, 1691, 1454, 1417, 1368,
1298, 1262, 1235, 1193, 1118, 756, 696; ¹H NMR (D₆-
DMSO) δ 8.59 (1*H*, d, *J* = 6.8), 8.48 (1*H*, s), 8.25-8.09
(3*H*, m), 7.85-7.75 (3*H*, m), 7.36 (5*H*, m), 5.39 (1*H*, m),
4.21 (2*H*, AB, *J* = 14.2), 4.53-4.49 (1*H*, m), 4.25-4.10
35 (2*H*, m), 3.65-3.44 (3*H*, m), 3.13-2.99 (1*H*, m), 2.43-
2.16 (1*H*, m), 1.72-0.72 (7*H*, m). Anal. Calcd for
C₃₀H₃₁N₅O₈S: C, 57.96; H, 5.03; N, 11.27. Found: C,
57.28; H, 5.14; N, 10.48. MS (ES⁺) 622.

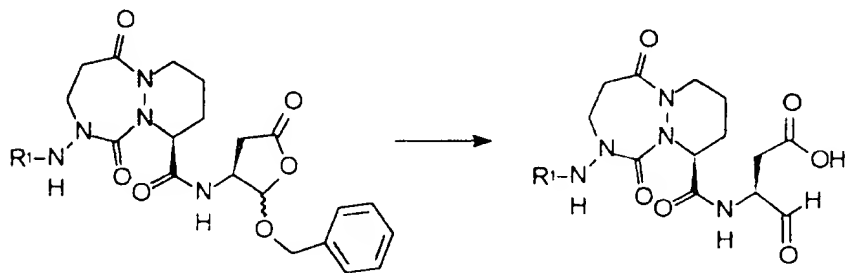
40 [4*S*(2*S*,3*S*)] *N*-(2-Benzoyloxy-5-oxo-tetrahydrofuran-3-yl)-
6,10-dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-
octahydro-6*H*-pyridazino[1,2-*a*][1,2,4]triazepine-1-
carboxamide (264c), was prepared by a similar method as
213e, (55%) as a colourless foam: mp. 135-40°C; [α]_D²²
+51.6° (c 0.1, CH₂Cl₂); IR (KBr) 3314, 1790, 1664,

- 668 -

compound	R ¹
264a 265a	
264c 265c	
264d 265d	
264e 1095	
264f 265f	
264g 1075	
264h 1018	
264i 1052	
264j 1027	

- 667 -

pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (2631). A suspension of 5251 (3.32g, 8.2mmol) in tetrahydrofuran (60ml) was treated with a solution of LiOH·H₂O (0.69g, 16.4mmol, 2.0 equiv) in water (20ml).
 5 The resulting mixture was stirred for 1h, concentrated and the residue dissolved in water (50ml). The solution was acidified using 2M. NaHSO₄ and the product extracted with EtOAc (100ml and 50ml portions). The combined extract was washed once with brine (2 x 50ml),
 10 dried (MgSO₄) and concentrated to afford 2631 as a white crystalline solid (2.87g, 90%): mp. 154-8°C; $[\alpha]_D^{20} +85.6^\circ$ (c 0.01, CH₃OH); IR (KBr) 3700-2300 (br), 3248, 2942, 1733, 1681, 1658, 1648, 1536, 1486, 1440, 1297, 1255, 1037; ¹H NMR (D₆-DMSO) δ 13.23 (1H, bs),
 15 10.45 (1H, s), 7.45 (1H, d), 7.35 (1H, s), 7.03 (1H, d), 6.12 (2H, s), 5.00-4.93 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H, m), 2.95-2.70 (1H, m), 2.40-2.25 (1H, m), 2.15-2.00 (1H, m), 1.91-1.40 (3H, m). Anal. Calcd for C₁₇H₁₈N₄O₇·0.8H₂O: C, 50.45; H, 4.88; N, 13.84.
 20 Found: C, 50.80; H, 4.95; N, 13.36. MS (ES⁺) 390 (M⁺, 19%), 389 (M⁺ - 1, 100), 345 (9), 204 (31), 182 (27), 111 (12).

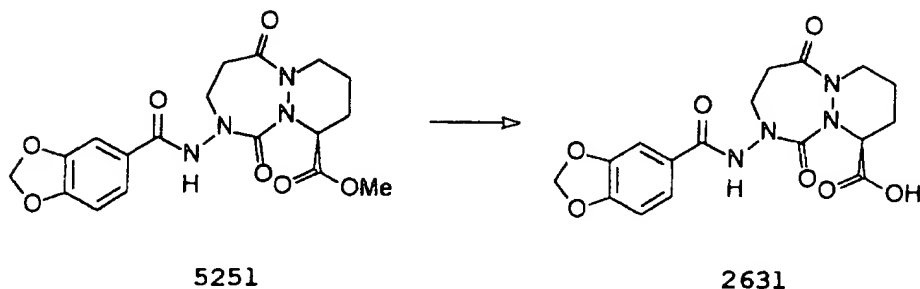


264a, c-1

 265a, c, d, f
 1015, 1018, 1027,
 1052, 1056, 1075, 1095

- 666 -

2945, 1738, 1650, 1611, 1501, 1445, 1309, 1255, 1171;
¹H NMR (CDCl₃) δ 9.35 (1H, s), 7.74 (2H, d), 7.38 (5H,
 m), 6.85 (2H, d), 5.40 (1H, bs), 5.19 (1H, s), 5.02
 (2H, s), 4.49 (1H, d), 3.92 (2H, m), 3.68 (1H, m), 2.99
 5 (1H, bs), 2.43 (1H, bs), 2.22 (1H, bs), 1.99 (1H, bs),
 1.68 (2H, bs).



(4S) Methyl 6,10-dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-
 10 6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate
 (5251), was synthesized via method used to prepare 211
 to afford a white crystalline solid (3.35g, 83%): mp.
 214-5°C; [α]_D²⁰ +75.2° (c 0.1, CH₂Cl₂); IR (KBr) 3272,
 2955, 1747, 1664, 1610, 1485, 1443, 1265, 1040; ¹H NMR
 15 (CDCl₃) δ 8.66 (1H, s), 7.32 (1H, dd), 7.23 (1H, d),
 6.76 (1H, d), 6.02 (2H, s), 5.20 (1H, dd), 4.55-4.45
 (1H, m), 4.03-3.70 (3H, m), 3.78 (3H, s), 3.05-2.88
 (1H, m), 2.47-2.35 (1H, m), 2.35-2.20 (1H, m), 2.10-
 1.90 (1H, m), 1.85-1.50 (2H, m). Anal. Calcd for
 20 C₁₈H₂₀N₄O₇•0.5H₂O: C, 52.87; H, 5.06; N, 13.70. Found:
 C, 52.84; H, 5.00; N, 13.66. MS (ES⁺) 406 (M⁺ + 2,
 20%), 405 (M⁺ + 1, 100), 391 (10), 162 (6), 148 (3),
 105 (2).

(4S) 6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-
 25 1,2,3,4,7,8,9,10-octahydro-6H-

- 665 -

(M⁺, 10%), 402 (M⁺ - 1, 100), 358 (10), 247 (10), 227 (16), 219 (51), 198 (12), 184 (17).

(4S) 6,10-Dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylic acid

5 (263i), was obtained as a white glassy solid (approx 100%) used without purification: ¹H NMR (CDCl₃) δ 9.23 (1H, s), 7.72 (2H, d, J = 8.8), 6.81 (2H, d, J = 8.9), 5.22 (1H, m), 4.51 (1H, m), 3.97-3.72 (2H, m), 3.81 (3H, s), 3.03 (1H, m), 2.51-2.46 (1H, m), 2.31-2.25
10 (1H, m), 2.03 (1H, m), 1.72 (2H, m).

(4S) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid

(263j), was obtained as a white solid (100%): mp. 73-
15 83°C (dec); [α]_D²² +104.7° (c 0.3, CH₂Cl₂); IR (KBr) 3600-2500 (br), 3208, 1734, 1666, 1481, 1448, 1416, 1338, 1311, 1214, 1171, 1091, 729, 689; ¹H NMR (CDCl₃) δ 7.87 (3H, m), 7.70-7.50 (3H, m), 7.16 (1H, brs), 4.99 (1H, m), 4.37 (1H, brd, J = 12.8), 3.92 (1H, m), 3.67
20 (2H, m), 2.36 (2H, m), 2.13 (1H, brd, J = 12.2), 1.56 (3H, m). Anal. Calcd for C₁₅H₁₈SN₄O₆•0.25CF₃CO₂H: C, 45.31; H, 4.48 N, 13.64. Found: C, 45.48; H, 4.71; N, 13.43. MS (ES⁺) 383 (MH⁺, 100%). Accurate mass calculated for C₁₅H₁₉SN₄O₆ (MH⁺): 383.1025. Found:
25 383.1007.

(4S) 7-(4-Benzyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263k), (100%) obtained: mp. 130-142°C; IR (KBr) 3272,

- 664 -

18.42. MS (ES^+) 361 (M^+ , 20%), 360 ($M^+ - 1$, 100), 241 (11), 240 (89), 196 (15), 175 (29), 111 (12).

(4S) 6,10-Dioxo-7-(indole-2-carboxamido)-
1,2,3,4,7,8,9,10-octahydro-6H-

- 5 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263g), was obtained as a white solid (259mg, 92%) mp.
248-51°C; $[\alpha]_D^{24} +94.0^\circ$ (c 0.01, CH_3OH); IR (KBr) 3700-
2300 (br) 3341, 2956, 1738, 1668, 1651, 1529, 1425,
1311, 1259, 751; 1H NMR (D_6 -DMSO) δ 13.29 (1H, bs),
10 11.72 (1H, s), 10.64 (1H, s), 7.65 (1H, d), 7.45 (1H,
d), 7.26-7.15 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m),
5.05-4.95 (1H, m), 4.40-4.25 (1H, m), 3.90-3.50 (3H,
m), 2.88-2.75 (1H, m), 2.38-2.20 (1H, m), 2.20-2.00
(1H, m), 1.90-1.35 (3H). Anal. Calcd for
15 $C_{18}H_{19}N_5O_5 \cdot 0.5H_2O$: C, 53.59; H, 5.25; N, 17.35. Found:
C, 53.66; H, 4.88; N, 17.11. MS (ES^+) 385 (M^+ , 23%),
384 ($M^+ - 1$, 100), 298 (6), 253 (8), 227 (10), 199
(23), 196 (10), 173 (9), 126 (21).

(4S) 7-[(4-Acetamido)benzamido]-6,10-dioxo-

- 20 1,2,3,4,7,8,9,10-octahydro-6H-
pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263h), was obtained as a white solid (282mg, 99%); mp.
210-5°C; $[\alpha]_D^{24} +74.5^\circ$ (c 0.01, CH_3OH); IR (KBr) 3700-
2300 (br) 3444, 3316, 2960, 1664, 1599, 1531, 1439,
25 1301, 1184; 1H NMR (D_6 -DMSO) δ 13.30 (1H, bs), 10.50
(1H, s), 10.25 (1H, s), 7.80 (2H, d), 7.68 (2H, d),
5.00-4.90 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H,
m), 2.88-2.70 (1H, m), 2.35-2.25 (1H, m), 2.25-1.95
(1H, m), 2.08 (3H, s), 1.95-1.35 (3H, m). MS (ES^+) 403

- 663 -

m), 7.97 (2H, m), 7.15-6.84 (3H, m), 5.29 (1H, m), 4.62 (1H, m), 4.04-3.65 (4H, m), 3.89 (3H, s), 2.92 (1H, m), 2.50 (1H, m), 2.30 (1H, m), 2.10-1.75 (2H, m).

(4S) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetyl-amino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263e), obtained as a white foamy solid (117mg, 98%): mp. 109-14°C; $[\alpha]_D^{24} +82.6^\circ$ (c 0.06, CH₂Cl₂); IR (KBr) 3700-2250 (br), 3437, 3274, 2959, 1733, 1664, 1481, 1437, 1310, 1177; ¹H NMR (CDCl₃) δ 7.99 (1H, s), 7.40-7.15 (5H, m), 5.15-5.10 (1H, m), 5.25-4.70 (1H, bs), 4.50-4.35 (1H, m), 3.95-3.50 (3H, m), 3.61 (2H, s), 2.93-2.78 (1H, m), 2.40-2.20 (2H, m), 2.10-1.80 (1H, m), 1.80-1.60 (2H, m). Anal. Calcd for C₁₇H₂₀N₄O₅·1H₂O: C, 53.96; H, 5.86; N, 14.81. Found: C, 54.12; H, 5.50; N, 14.68. MS (ES⁺) 360 (M⁺, 21%), 359 (M⁺ - 1, 100), 196 (14), 182 (14), 111 (7).

(4S) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263f), obtained as a white foamy solid (199mg, 92%): mp. 149-52°C; $[\alpha]_D^{24} +92.0^\circ$ (c 0.01, CH₃OH); IR (KBr) 3700-2300 (br), 3319, 2956, 1726, 1664, 1600, 1548, 1500, 1444, 1313, 1238, 755; ¹H NMR (D₆-DMSO) δ 8.90 (1H, s), 8.24 (1H, s), 7.42 (2H, d), 7.30-7.20 (2H, m), 7.00-6.90 (1H, m), 4.98-4.92 (1H, m), 4.32-4.22 (1H, m), 3.80-3.55 (3H, m), 2.85-2.70 (1H, m), 2.30-2.20 (1H, m), 2.20-2.00 (1H, m), 1.90-1.35 (3H, m). Anal. Calcd for C₁₆H₁₉N₅O₅·0.75H₂O: C, 51.26; H, 5.51; N, 18.68. Found: C, 51.11; H, 5.23; N,

- 662 -

2.01 (1H, m), 1.91-1.83 (1H, m), 1.46-1.26 (1H, m),
1.13-1.06 (1H, m), 0.90-0.77 (1H, m). MS (ES⁺) 431.

(4S) 7-(Benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-

- 5 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263b). 200mg (100%) was obtained as a white solid:
mp. 155°C; $[\alpha]_D^{20} +13^\circ$ (c 0.07, CH₂Cl₂); IR (KBr) 3431,
2935, 1734, 1663, 1531, 1435, 1292, 1177; ¹H NMR
(CDCl₃) δ 9.73 (1H, bs), 7.73-7.27 (5H, m), 5.35-5.25
10 (1H, m), 4.56-4.48 (1H, m), 4.05-3.65 (3H, m), 3.12-
3.00 (1H, m), 2.50-2.45 (1H, m), 2.30-2.20 (1H, m),
2.10-2.00 (1H, m), 1.75-1.61 (2H, m). MS (ES⁺) 401.

(4S) 6,10-Dioxo-7-(3-methoxyphenylureido)-
1,2,3,4,7,8,9,10-octahydro-6H-

- 15 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263c), 216mg, (100%) obtained as a colourless foam:
 $[\alpha]_D^{23} 32.5^\circ$ (c 0.1, CH₂Cl₂); IR (KBr) 3326, 1730,
1661, 1610, 1555, 1495, 1431, 1314, 1288, 1217, 1175,
1161; ¹H NMR (CDCl₃) δ 7.87 (1H, s), 7.58 (1H, s), 7.19
20 (2H, m), 6.82 (1H, m), 6.62 (1H, m), 5.21 (1H, m), 4.55
(1H, m), 3.76 (3H, s), 4.0-3.65 (4H, m), 2.85 (1H, m),
2.35 (2H, m), 1.75 (1H, m), 1.71 (2H, m).

(4S) 6,10-Dioxo-7-(2-methoxyphenylureido)-
1,2,3,4,7,8,9,10-octahydro-6H-

- 25 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263d), (100%) obtained as colourless foam: $[\alpha]_D^{24}$
+11.7° (c 0.1, CH₂Cl₂); IR (KBr) 3394, 3325, 1666,
1603, 1543, 1490, 1463, 1438, 1329, 1311, 1292, 1249,
1214, 1176, 1119, 1024, 752; ¹H NMR (CDCl₃) δ 8.15 (1H,

- 661 -

IR (KBr) 3283, 1732, 1684, 1448, 1430, 1404, 1369, 1338, 1306, 1285, 1242, 1169, 1091, 692; ^1H NMR (CDCl_3) δ 7.89 (2H, d, $J = 7.4$), 7.76 (1H, s), 7.64-7.49 (3H, m), 4.83 (1H, m), 4.35 (1H, brd, $J = 13.0$), 4.00 (1H, m), 3.74-3.63 (2H, m), 2.39-2.26 (2H, m), 2.06 (1H, m), 1.50-1.41 (10H, m). Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_6$: C, 52.04; H, 5.98; N, 12.78. Found: C, 52.11; H, 5.95; N, 12.71. MS (ES^+) 437 ($\text{M}^+ - 1$, 100%).

(3S) t-Butyl (7-(4-benzyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262k), (83%) was obtained: $[\alpha]_{\text{D}}^{22} +42.3^\circ$. (c 0.11, CH_2Cl_2); IR (KBr) 3287, 2997, 2935, 1735, 1681, 1606, 1501, 1296, 1248, 1173, 1155. ^1H NMR (CDCl_3) δ 9.23 (1H, s), 7.73 (2H, d), 7.38 (5H, m), 6.85 (2H, d), 5.08 (1H, m), 5.02 (2H, s), 4.48 (1H, bd), 4.15-3.65 (3H, m), 2.96 (1H, m), 2.45-2.10 (2H, m), 1.88 (1H, m), 1.63 (2H, m), 1.48 (9H, s). M.S. (ES^+) 509 ($\text{M}^+ + 1$).

Compounds 263a-k were synthesized via methods used to prepare 212b-f.

(4S) 6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263a), 348mg (94%) obtained as a white foamy solid: mp. $[\alpha]_{\text{D}}^{21} +171^\circ$ (c 0.056, CH_2Cl_2); IR (KBr) 3426, 3233, 2953, 1734, 1663, 1481, 1415, 1340, 1214, 1167, 1132, 1075, 668; ^1H NMR (CDCl_3) δ 8.44 (1H, s), 8.00-7.60 (7H, m), 4.85-4.83 (1H, m), 4.25-4.00 (1H, m), 4.07-3.90 (1H, m), 3.70-3.46 (2H, m), 2.38-2.30 (1H, m), 2.12-

- 660 -

(4S) t-Butyl 7-[(4-acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxylate (262h), was obtained as a white solid (325mg, 73%): mp. 209-12°C; $[\alpha]_D^{24} +62.4^\circ$ (c 0.2, CH₂Cl₂); IR (KBr) 3513, 3269, 2980, 1731, 1680, 1653, 1599, 1531, 1314, 1158; ¹H NMR (CDCl₃) δ 9.40 (1H, s), 8.75 (1H, s), 7.72 (2H, d), 7.47 (2H, d), 5.15-5.05 (1H, m), 4.55-4.45 (1H, m), 4.05-3.70 (3H, m), 3.00-2.80 (1H, m), 2.45-2.35 (1H, m), 2.30-2.15 (1H, m), 2.10 (3H, s), 2.00-1.80 (1H, m), 1.80-1.50 (2H, m), 1.48 (9H, s). Anal. Calcd for C₂₂H₂₉N₅O₆: C, 57.51; H, 6.36; N, 15.24. Found: C, 57.41; H, 6.38; N, 15.12. MS (ES⁺) 461 (M⁺ + 2, 26%), 460 (M⁺ + 1, 100), 405 (12), 404 (55), 354 (7), 285 (23), 229 (52), 183 (22).

15 (4S) t-Butyl 6,10-dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylate (262i), was obtained as a white glassy solid (76%): mp. 85-9°C; $[\alpha]_D^{25} +66.4^\circ$ (c 0.11, CH₂Cl₂); IR (KBr) 1732, 1668, 1607, 1502, 1440, 1312, 1295, 1258, 1176, 1157, 1025; ¹H NMR (CDCl₃) δ 8.25 (1H, s), 7.77 (2H, m), 6.90 (2H, m), 5.11-5.07 (1H, m), 4.55-4.48 (1H, m), 4.01-3.91 (2H, m), 3.86-3.78 (1H, m), 3.85 (3H, s), 2.98 (1H, m), 2.46-2.40 (1H, m), 2.26-2.20 (1H, m), 2.05-1.80 (1H, m), 1.70-1.64 (2H, m), 1.48 (9H, s).

(4S) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262j), was obtained as a white crystalline solid 30 (79%): mp. 182-3°C (dec); $[\alpha]_D^{22} +92.1^\circ$ (c 0.4, CH₂Cl₂);

- 659 -

(4S) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262f), was obtained as a white solid (273mg, 93%): mp. 102-6°C; $[\alpha]_D^{22} +7.5^\circ$ (c 0.07, CH₂Cl₂); IR (KBr) 3320, 2979, 1731, 1676, 1669, 1601, 1549, 1444, 1314, 1240, 1156; ¹H NMR (CDCl₃) δ 7.37-7.20 (6H, m), 7.08-6.98 (1H, m), 5.12 (1H, dd), 4.64-4.55 (1H, m), 4.02-3.78 (2H, m), 3.75-3.65 (1H, m), 2.94-2.75 (1H, m), 2.57-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.50 (3H, m), 1.48 (9H, s). Anal. Calcd for C₂₀H₂₇N₅O₅•0.4H₂O: C, 56.56; H, 6.60; N, 16.49. Found: C, 56.89; H, 6.58; N, 16.07. MS (ES⁺) 419 (M⁺ + 2, 24%), 418 (M⁺ + 1, 100), 363 (15), 362 (81), 242 (10).

(4S) t-Butyl 6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262g), (13g) was obtained as a white solid (298mg, 70%): mp. 138-43°C; $[\alpha]_D^{23} +69.8^\circ$ (c 0.1, CH₂Cl₂); IR (KBr) 3282, 2978, 1733, 1664, 1536, 1421, 1310, 1156, 748; ¹H NMR (CDCl₃) δ 9.67 (1H, s), 9.53 (1H, s), 7.50 (1H, d), 7.30-7.15 (2H, m), 7.10-7.00 (1H, m), 6.93 (1H, s), 5.16-5.12 (1H, m), 4.60-4.50 (1H, m), 4.05-3.85 (2H, m), 3.85-3.70 (1H, m), 3.05-2.90 (1H, m), 2.55-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.85 (1H, m), 1.85-1.50 (2H, m), 1.47 (9H, s). Anal. Calcd for C₂₂H₂₇N₅O₅•0.45H₂O: C, 58.77; H, 6.26; N, 15.58. Found: C, 59.14; H, 6.24; N, 15.18. MS (ES⁺) 433 (M⁺ + 2, 26%), 442 (M⁺ + 1, 100), 387 (17), 386 (79), 285 (20), 229 (85), 211 (26), 185 (15), 183 (57), 139 (9).

- 658 -

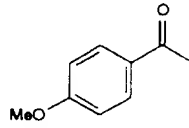
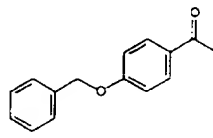
$[\alpha]_D^{22} +22.6^\circ$ (c 0.1, CH_2Cl_2); IR (KBr) 3316, 1732, 1671, 1609, 1551, 1495, 1455, 1432, 1316, 1288, 1245, 1218, 1158, 1122, 1023; ^1H NMR (CDCl_3) δ 7.16 (4H, m), 6.79 (1H, m) 6.60 (1H, m), 5.11 (1H, m), 4.59 (1H, m),
5 3.89 (2H, m), 3.77 (3H, s), 3.72 (2H, m), 2.85 (1H, m).

(4S) t-Butyl 6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262d), (81%) was obtained as colourless foam: $[\alpha]_D^{22} +3.7^\circ$ (c 0.1, CH_2Cl_2); IR (KBr) 3468, 3446, 3269, 1734, 1698, 1667,
10 1609, 1555, 1490, 1461, 1433, 1423, 1296, 1246, 1215, 1173, 1157, 1028, 756; ^1H NMR (CDCl_3) δ 8.23 (1H, m), 7.95 (1H, s), 6.95 (4H, m), 5.15 (1H, m), 4.60 (1H, m), 3.98-3.65 (4H, m), 3.89 (3H, s), 2.90 (1H, m), 2.48
15 (1H, m), 2.25 (1H, m), 2.05-1.65 (2H, m), 1.48 (9H, s).

(4S) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262e), was obtained as a white foamy solid (155mg, 53%): mp. $53-7^\circ\text{C}$; $[\alpha]_D^{22} +57.4^\circ$ (c 0.1, CH_2Cl_2); IR (KBr) 3271, 2978, 1733, 1680, 1437, 1314, 1245, 1156;
20 ^1H NMR (CDCl_3) δ 7.46 (1H, s), 7.42-7.20 (5H, m), 5.03 (1H, dd), 4.52-4.40 (1H, m), 3.96-3.70 (2H, m), 3.70-3.49 (1H, m), 3.63 (2H, s), 2.92-2.75 (1H, m), 2.43-
25 2.33 (1H, m), 2.33-2.15 (1H, m), 2.00-1.50 (3H, m), 1.45 (9H, s). Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{N}_4\text{O}_5 \cdot 0.25\text{H}_2\text{O}$: C, 59.91; H, 6.82; N, 13.31. Found: C, 60.19; H, 6.80; N, 13.30. MS (ES^+) 418 ($\text{M}^+ + 2$, 25%), 417 ($\text{M}^+ + 1$, 100), 362 (9), 361 (45).

- 657 -

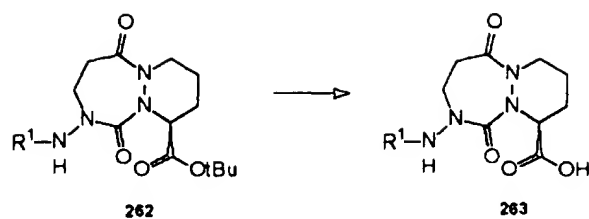
20

262i 263i	
262j 263j	PhSO ₂ —
262k 263k	

25 (4S) t-Butyl 6,10-dioxo-7-(2-naphthyl)sulfonamide-
1,2,3,4,7,8,9,10-octahydro-6H-
pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate
(262a). 443mg (91%) of the title compound was
obtained: mp. 56-7°C; $[\alpha]_D^{25} +76^\circ$ (c 0.15, CH₂Cl₂); IR
30 (KBr) 3429, 2979, 1734, 1675, 1418, 1369, 1339, 1323,
1244, 1164, 665; ¹H NMR (CDCl₃) δ 8.45 (1H, s), 8.00-7.59
(7H, m), 4.69-4.65 (1H, m), 4.25-4.12 (1H, m), 4.10-
3.99 (1H, m), 3.73-3.55 (2H, m), 2.40-2.30 (1H, m),
1.99-1.91 (1H, m), 1.82-1.62 (2H, m), 1.48-1.46 (2H,
35 m), 1.37 (9H, s). Anal. Calcd for C₂₃H₂₈N₄O₆S•H₂O: C,
54.53; H, 5.97; N, 11.06. Found: C, 54.60; H, 5.73; N,
10.95. MS (ES⁺) 489.

(4S) t-Butyl 6,10-dioxo-7-(3-methoxyphenylureido)-
1,2,3,4,7,8,9,10-octahydro-6H-
40 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate
(262c), 120mg (80%) of colourless foam was obtained:

- 656 -



262a-k

263a-k

compound	R
262a 263a	
262b 263b	
262c 263c	
262d 263d	
262e 263e	
262f 263f	
262g 263g	
262h 263h	

- 655 -

522 (7.15g, 19.1mmol) was dissolved in dichloromethane(100ml), containing dimethylformamide (0.5ml), and cooled to 0°C. Thionyl chloride (1.6ml, 2.61g, 22mmol) and N-ethyl morpholine (4.86ml, 440mg, 38.2mmol) were added and the mixture stirred for 2h. The organic mixture was washed with 2M sodium bisulphate (50ml), saturated sodium bicarbonate (50ml) and brine (50ml), dried (MgSO₄) and concentrated. The residues were triturated with ether to give 523 as a white solid (5.73g, 84%): mp. 186-188°C (decomp); $[\alpha]_D^{22} +65.3^\circ$ (c 0.25, CH₂Cl₂); IR (KBr) 3298, 2978, 1750, 1720, 1682, 1658, 1455, 1423, 1369, 1316, 1241, 1212, 1160; ¹H NMR (CDCl₃) δ 6.56 (1H, s), 5.17 (1H, dd), 4.48 (1H, bd), 3.81 (3H, m), 3.75 (3H, s), 2.83 (1H, dt), 2.40 (1H, m), 2.28 (1H, m), 1.95 (1H, m), 1.67 (1H, m), 1.47 (9H, s). Anal. Calcd for C₁₅H₂₄N₄O₆•1/6H₂O: C, 50.13; H, 6.82; N, 15.59. Found: C, 50.12; H, 6.71; N, 15.58. MS (ES⁺) 357 (M⁺ - 1, 46%), 301 (100%).

(4S) Methyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (524), was synthesized from 523 via method used to prepare 518.

Compounds 262a-k were synthesized via methods used to prepare 211b-f.

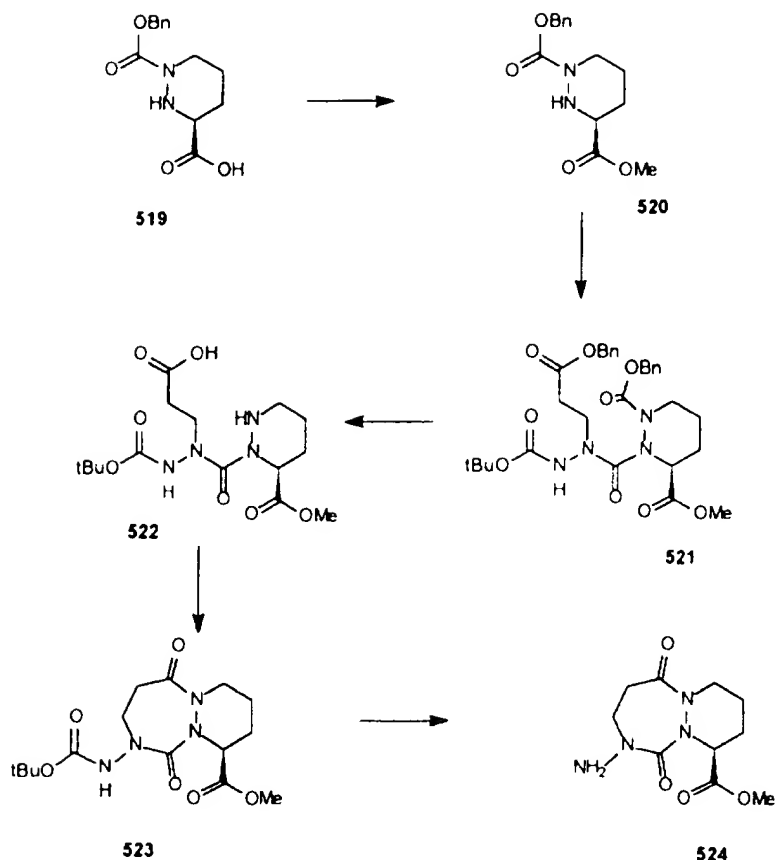
- 654 -

bd), 3.73 (3H, s), 3.55 (1H, dd), 3.12 (1H, t), 2.06 (1H, m), 1.73 (3H, m). Anal. Calcd for $C_{14}H_{17}N_2O_4 \cdot 0.25H_2O$: C, 59.46; H, 6.59; N, 9.91. Found: C, 59.44; H, 6.46; N, 10.09.

- 5 (3S) 1-Benzyl 3-methyl 2-(N-2-benzyloxycarbonylethyl-NI-t-butoxycarbonylhydrazino)carbonyl hexahydropyridazine dicarboxylate (521). Using a similar method to that described for 260 above, 521 was prepared, 96% as a crude oil: $[\alpha]_D^{22} -22.16^\circ$ (c 0.25, CH₂Cl₂); IR (film) 3316, 2976, 2953, 1738, 1726, 1714, 1690, 1367, 1260, 1167; ¹H NMR (CDCl₃) δ 7.25 (10H, m), 6.82 (1H, bs), 5.10 (4H, m), 4.80 (1H, bs), 4.3-3.4 (6H, m), 3.10 (1H, m), 2.59 (2H, m), 1.95 (2H, m), 1.44 (10H, m + s).
- 10
- 15 (3S) Methyl 2-(N'-t-butoxycarbonyl-N-2-carboxyethylhydrazino)-carbonyl hexahydropyridazine 3-carboxylate (522). Using a similar method to that described for 261 above, 522 was prepared, 92% as a white solid: mp. 146-148°C (decomp); $[\alpha]_D^{22} +27.8^\circ$ (c 0.25, CH₂Cl₂); IR (KBr) 3346, 1740, 1710, 1626, 1497, 1290, 1250, 1206, 1179, 1159; ¹H NMR (CDCl₃) δ 7.60 (1H, bs), 7.5-5.5 (1H, vbs), 4.64 (1H, bs), 3.76 (5H, m + s), 3.00 (1H, m), 2.70 (3H, m), 2.16 (1H, m), 1.92 (1H, m), 1.56 (1H, m), 1.46 (11H, m + s). Anal. Calcd for $C_{15}H_{26}N_4O_7$: C, 48.12; H, 7.00; N, 14.96. Found: C, 48.21; H, 6.96; N, 14.86. MS (ES⁺) 373 (M⁺ - 1).
- 20
- 25

(4S) Methyl 7-t-butoxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (523).

- 653 -



(3S) Methyl 1-benzyloxycarbonyl-hexahydropyridazine-3-carboxylate (520). 519 (9.4g, 35.6mmol) was suspended in methanol (230ml) and cooled to 0°C in an ice bath. Thionyl chloride (3ml, 4.89g, 41.1mmol) was added dropwise over 30min and the mixture stirred at ambient temperature for 48h. The solvent was removed in vacuo at 30°C and the oily residue dissolved in ethyl acetate (500ml). The organic solution was washed with saturated sodium bicarbonate, water and brine, dried (MgSO₄) and concentrated to give **520** (7.84g, 79%) as an oil: $[\alpha]_D^{22}$ -25.9° (c 0.615, CH₂Cl₂); IR (film) 2953, 1739, 1703, 1694, 1440, 1403, 1357, 1261, 1241, 1174; ¹H NMR (CDCl₃) δ 7.36 (5H, s), 5.18 (2H, s), 4.00 (1H,

- 652 -

pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate

(262b), was synthesized via method used to prepare 262 from 261 to give the title compound 262b, (18.6g, 54%)

as an oil: $[\alpha]_D^{20} +47.7^\circ$ (c 0.236, CH_2Cl_2); IR (film)

5 3291, 2978, 1738, 1727, 1690, 1678, 1439, 1243, 1164;

^1H NMR (CDCl_3) δ 6.59 (1H, s), 5.06 (1H, m), 4.47 (1H, m), 3.85 (3H, m), 2.82 (1H, m), 2.37 (1H, m), 2.22 (1H, m), 1.92 (1H, m), 1.63 (2H, m), 1.48 and 1.46 (18H, 2 x s). MS (ES^+) 399 ($\text{M}^+ + 1$).

- 10 (4S) t-Butyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (518). Compound 262b (2.43g, 6.1mmol) was dissolved in 1M hydrogen chloride in ethyl acetate (30ml) and stirred at room temperature for 20h. Solid
- 15 sodium bicarbonate (4g, 46.5mmol) and water 20ml were added and the mixture stirred for 5min before separating and extracting the aqueous portion with ethyl acetate. The combined organic solution was washed with water, saturated salt, dried (MgSO_4) and
- 20 concentrated. Purification by flash chromatography (50% ethyl acetate in dichloromethane - 100% ethyl acetate) gave the pure product 518 (1.08g, 59%) as an unstable oil: $[\alpha]_D^{20} +82^\circ$ (c 0.55, CH_2Cl_2); IR (film) 3331, 2977, 1731, 1680, 1664, 1439, 1420, 1315, 1158;
- 25 ^1H NMR (CDCl_3) δ 5.08 (1H, m), 4.48 (1H, m), 3.80 (2H, Abc), 3.70 (2H, bs, exch with D_2O), 3.53 (1H, m), 2.75 (1H, m), 2.30 (2H, m), 1.88 (1H, m), 1.71 (2H, m), 1.47 (9H, s).

- 651 -

1254, 1171; ^1H NMR (CDCl_3) δ 7.35 (5H, m), 6.15 (1H, bs),
5.13 (2H, s), 3.15 (2H, t, $J = 6.5$), 2.54 (2H, t, $J =$
6.5), 1.45 (9H, s). Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3$: C,
61.21; H, 7.53; N, 9.52. Found: C, 61.29; H, 7.51; N,
5 9.51. MS (ES^+) 295 ($\text{M}^+ + 1$).

(3S) 1-Benzyl 3-*t*-butyl 2-(N-2-benzyloxycarbonylethyl-
NI-2-butoxycarbonylhydrazino) carbonyl
hexahydropyridazine dicarboxylate (260b), was
synthesized via method used to prepare 260 from 259 to
10 afford a gum (81g) which was used in the next step
without purification. Analytical data for a pure
sample: IR (film) 3318, 2976, 1733, 1451, 1412, 1393,
1366, 1256, 1161; ^1H NMR (CDCl_3) δ 7.34 (10H, m), 6.68
(0.5H, bs), 5.11 (4H, m), 4.63 (0.5H, bs), 4.14 (1H,
15 m), 3.53 (2H, m), 3.08 (1H, m), 2.63 (2H, m), 2.10-1.60
(4H, m), 1.60-1.35 (19H, m + 2 x s).

(3S) *t*-Butyl 2-(N'-*t*-butoxycarbonyl-N-2-
carboxyethylhydrazino)-carbonylhexahydropyridazine 3-
carboxylate (261b), was synthesized via method used to
20 prepare 261 from 260 to give a gum which was purified
by flash chromatography (1:1 ethyl
acetate/dichloromethane) to give the title compound
261b (36.0g, 79.4% over 2 stages): IR (film) 3267,
2979, 2937, 1728, 1668, 1394, 1369, 1245, 1159; ^1H NMR
25 (CDCl_3) δ 7.6 (1H, bs), 6.8 (1H, vbs), 4.47 (1H, bs),
3.73 (2H, bs), 2.98 (1H, bs), 2.66 (3H, m), 2.04 (1H,
bs), 1.84 (1H, m), 1.6-1.2 (21H, m + s).

(4S) *t*-Butyl 7-*t*-butoxycarbonylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-

- 650 -

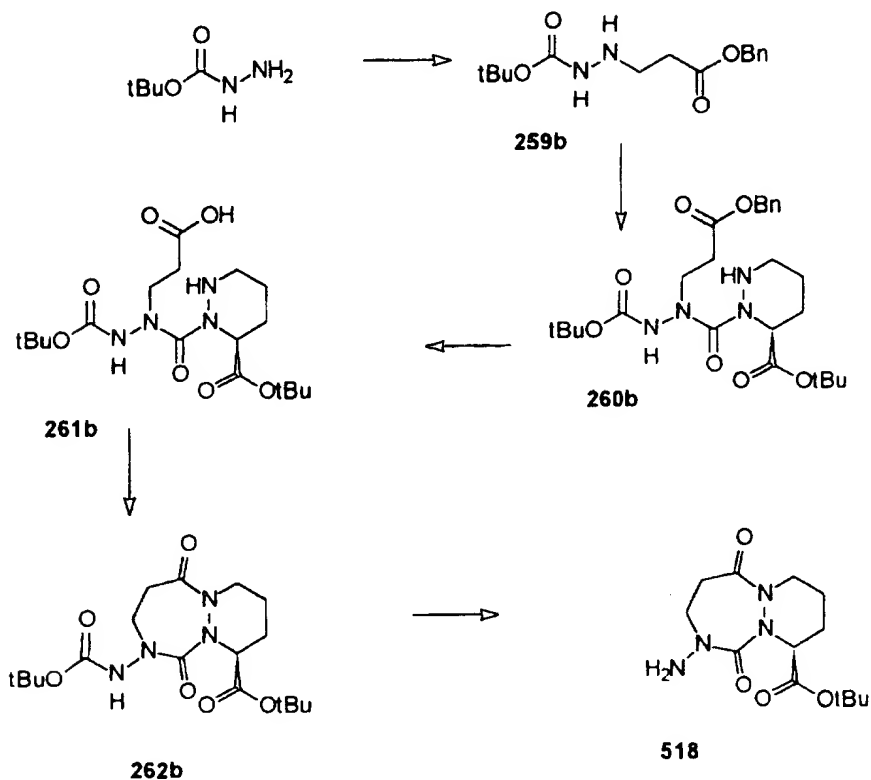
Analytical HPLC methods:

(1) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm).

Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

5 (2) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm).

Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.



Benzyl 3-(N'-t-butyloxycarbonylhydrazino)propionate (259b), was synthesized via method used to prepare 259 from 258 to afford a waxy solid (87g, 51%): mp 54-55°C; IR (film) 3324, 2978, 1732, 1713, 1455, 1367, 1277,

- 649 -

dimethylformamide (3 X 1 mL) and N-methylpyrrolidone (3 X 1 mL).

Resin 1103 was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBT in N-methylpyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methylpyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), dichloromethane (5 X 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H₂O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 ether:hexane (10 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H₂O/0.1% TFA (5 mL) and lyophilized to obtain crude 1105-1125 as a white powder. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (8% - 48%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide 1105-1125 (10.8 mg, 63%).

- 648 -

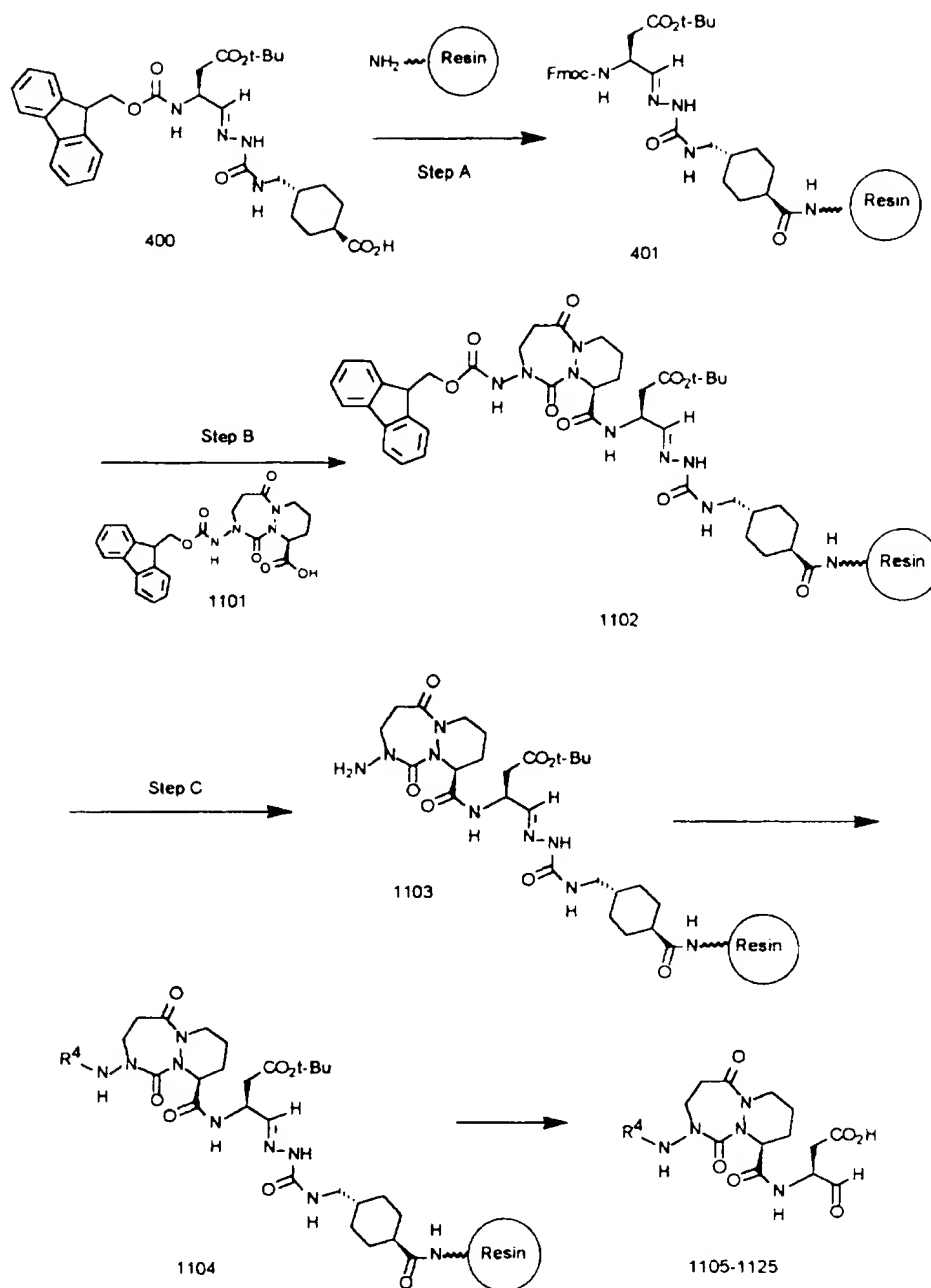
dissolved in DMA (10 mL) and O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 0.88 g, 2.3 mmol), and DIEA (0.8 mL, 4.6 mmol) were added. The solution was transferred to the resin and a further 5 mL DMA added. The reaction mixture was agitated for 1.5 h at room temperature using a wrist arm shaker. The resin was filtered and washed with dimethylacetamide (4 X 15 mL).

Step B. Synthesis of 1102. Resin 401 was deprotected with 20% (v/v) piperidine/dimethylacetamide (15 mL) for 10 min (shaking) and then for 10 min with fresh piperidine reagent (15 mL). The resin was then washed with dimethylacetamide (6 X 15 mL), followed by N-methylpyrrolidone (2 X 25 mL).

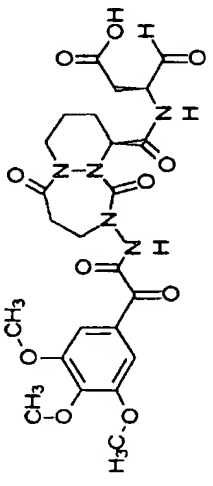
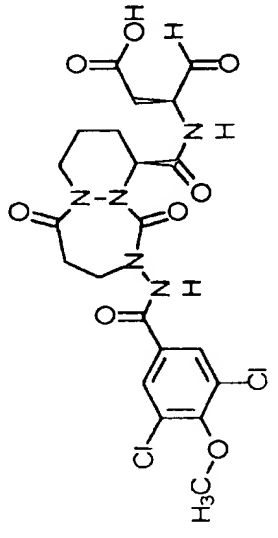
Compound 1101 (0.979 g, 2.11 mmol) was dissolved in dimethylacetamide (8 mL). HBTU (0.81 g, 2.1 mmol) and DIEA (0.75 mL, 4.3 mmol) were added and the solution added to the resin, followed by dimethylacetamide (4 mL). The reaction mixture was agitated for 2 h at room temperature using a wrist arm shaker. The resin work-up was performed as described for 401 to yield 1102.

Step C. Synthesis of 1103. This compound was prepared from resin 1102 (0.040 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (2 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin 1103. The resin was washed with

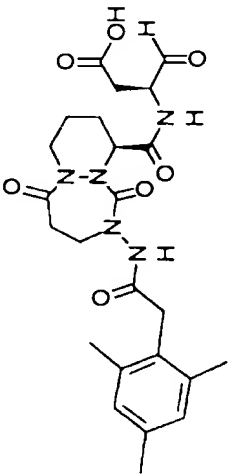
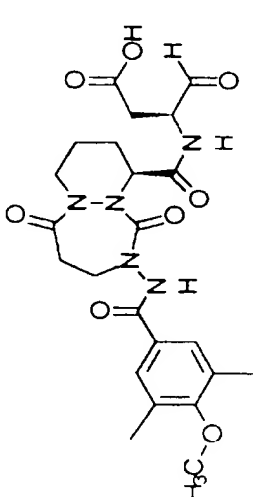
- 647 -

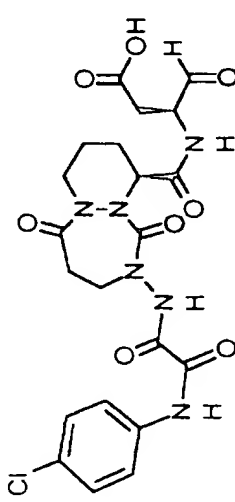
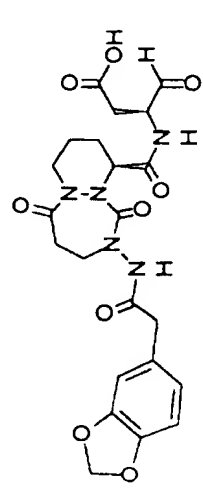


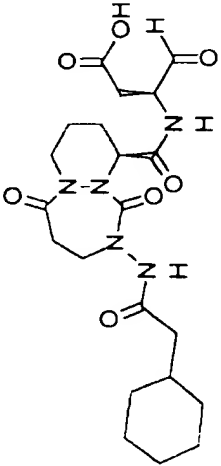
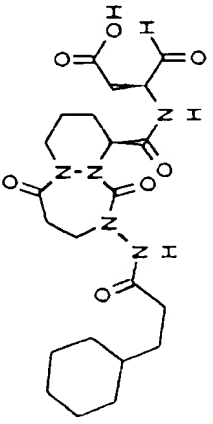
Step A. Synthesis of 401. TentaGel S S NH_2 resin (0.25 mmol/g, 5.25 g) was placed in a sintered glass shaker vessel and washed with dimethylacetamide (3 X 15 mL). Compound **400** (1.36 g, 2.3 mmol) was

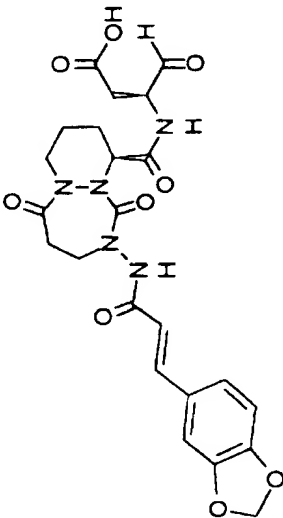
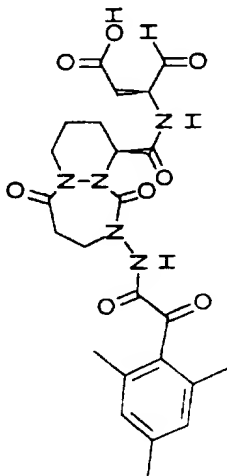
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1124		C ₂₄ H ₂₉ N ₅ O ₁₁	563.53	13.336 (1) 99%	587
1125		C ₂₁ H ₂₃ Cl ₂ N ₅ O ₈	544.35	8.99 0.95	566

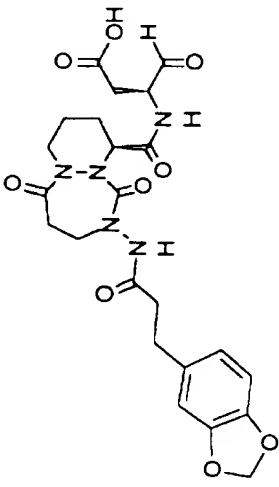
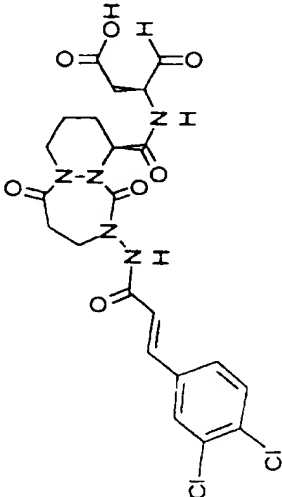
- 645 -

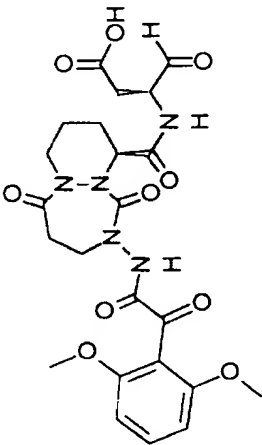
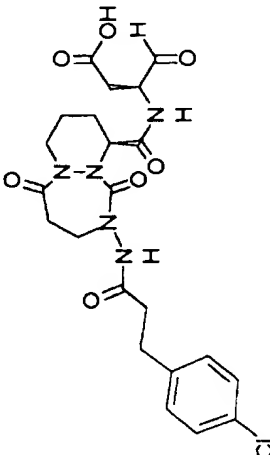
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1122		C ₂₄ H ₃₁ N ₅ O ₇	501.54	10.892 (2) 98%	525.5
1123		C ₂₆ H ₂₄ N ₄ O ₁₀	552.50	15.85 >0.98	574

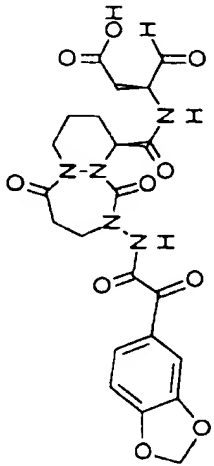
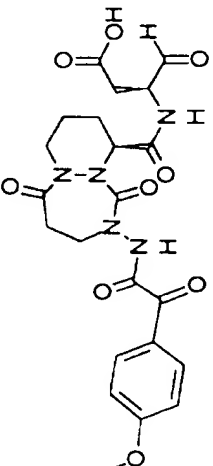
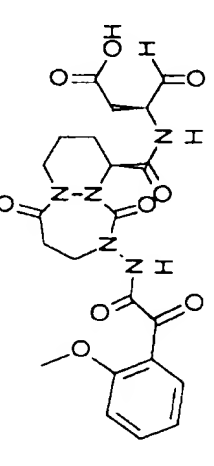
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1120		C21H23ClN6O8	522.91	16.796 (1) 99%	547.3
1121		C22H25N5O9	503.47	11.131 (1) 99%	527.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1118		C ₂₁ H ₃₁ N ₅ O ₇	465.51	13.974 (1) 96%	488.9
1119		C ₂₂ H ₃₃ N ₅ O ₇	479.54	11.079 (2) 95%	502.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1116		C23H25N5O9	515.48	14.144 (1) 85%	538.8
1117		C24H29N5O8	515.53	11.551 (2) 97%	538.8

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1114		C23H27N5O9	517.50	12.902 (1) 99%	542.4
1115		C22H23Cl2N5O7	540.36	12.529 (2) 97%	563.4

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1112		C23H27N5O10	533.50	11.377 (1) 98%	557.2
1113		C22H26ClN5O7	507.93	16.317 (1) 98%	531.5

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1109		C22H23N5O10	517.46	12.341 (1) 92%	541.2
1110		C22H25N5O9	503.47	12.991 (1) 96%	527.9
1111		C22H25N5O9	503.47	10.951 (1) 99%	526.7

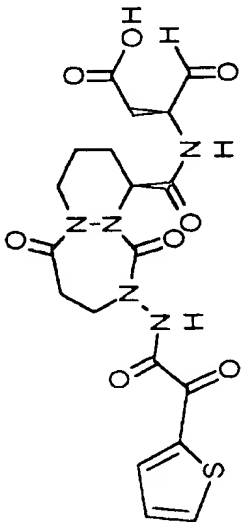
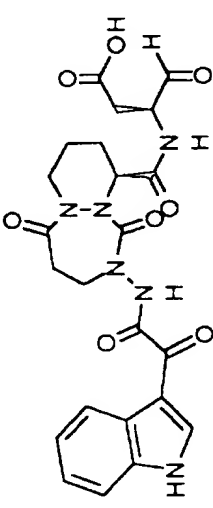
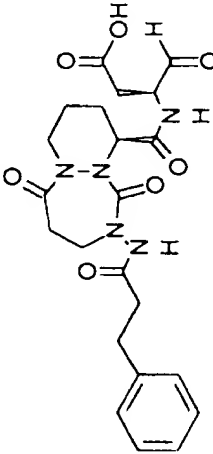
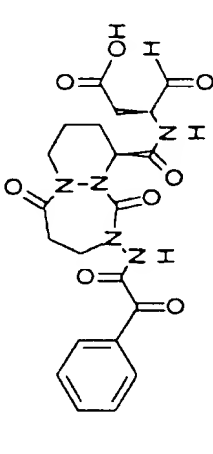
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1107		C19H21N5O8S	479.47	11.272 (1) 97%	502.9
1108		C23H24N6O8	512.48	13.699 (1) 97%	536.4

Table 24

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1105		C22H27N5O7	473.49	12.769 (1) 99%	496.9
1106		C21H23N5O8	473.45	12.137 (1) 99%	496.9

- 636 -

(3S,4R) t-Butyl 3-(allyloxycarbonylamino)4,5-dihydroxy pentanoate (517). A solution 516 (2.44g, 7.41mmol) in 80% aqueous acetic acid (25ml) was stirred at room temperature for 24h then concentrated and azeotroped with toluene (2 x 25ml). The residue was treated with brine (25ml) and extracted with ethylacetate (2 x 25ml). The organic fractions were dried (MgSO₄) and concentrated to afford a colourless oil. Flash chromatography (20-80% ethyl acetate in dichloromethane) gave a colourless solid (1.99g, 90%): mp. 74-5°C; $[\alpha]_D^{25}$ -1.3° (c 1.0, CH₂Cl₂); IR (KBr) 1723, 1691; ¹H NMR (CDCl₃) δ 6.02-5.78 (2H, m), 5.35-5.16 (2H, m), 4.55 (2H, d), 4.16-4.04 (2H, m), 2.76 (2H, s), 3.56 (2H, m), 2.56 (2H, m), 1.43 (9H, s); Anal. Calcd for C₁₃H₂₃NO₆ : C, 53.97; H, 8.01; N, 4.84. Found : C, 53.79; H, 7.88; N, 4.81; MS(+FAB) 290 (M⁺+1, 44%), 234 (100).

Example 30

Compounds 1105-1125 were prepared as follows.

Physical data for these compounds is listed in Table 24.

- 635 -

Tetrahedron Letters 24, pp. 3009-3012 (1983) as a pure diastereomer (60%) as an oil: $[\alpha]_D^{23} -36.9^\circ$ (c 0.5, dichloromethane); IR (film) 2982, 2934, 1726, 1455, 1369, 1257, 1214, 1157, 1068; ^1H NMR (CDCl_3) δ 7.31 (5H, m), 4.10 (1H, q, $J = 6.0$), 4.05-3.75 (4H, m), 3.10 (1H, q, $J = 6.0$), 2.40 (2H, m), 1.42 (9H, s), 1.40 (3H, s), 1.34 (3H, s).

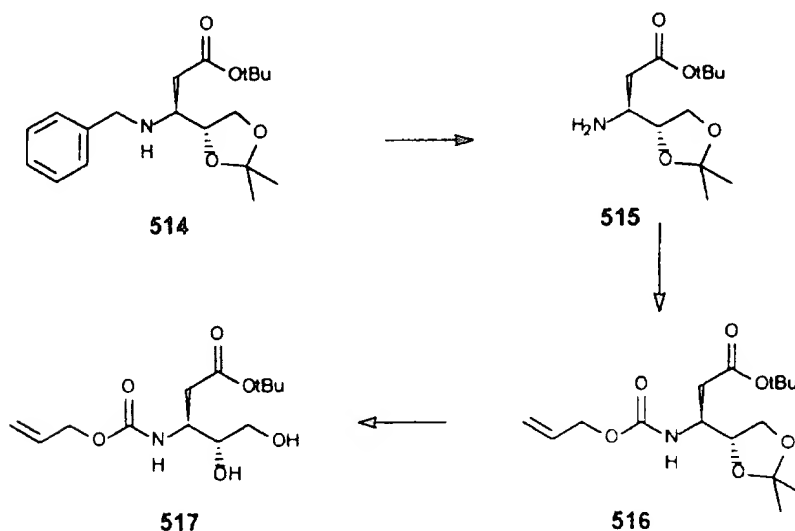
(3S,4R) t-Butyl 3-(allyloxycarbonylamino)-4,5-(dimethylmethylenedioxy)pentanoate (516). 514 (3.02g, 9.00mmol) and 10% palladium on carbon (300mg) in ethanol (30ml) were stirred under hydrogen for 2h. The suspension was filtered through celite and a 0.45mm membrane and the filtrate concentrated to give a colourless oil 515 (2.106g, 95%) which was used without purification. The oil (1.93g, 7.88mmol) was dissolved in water (10ml) and 1,4-dioxan and sodium hydrogen carbonate added (695mg, 8.27mmol). The mixture was cooled to 0°C and allyl chloroformate (1.04g, 9.19ml, 8.66mmol) added dropwise. After 3h the mixture was extracted with ether (2 x 50ml). The combined ether extracts were washed with water (2 x 25ml) and brine (25ml), dried (MgSO_4) and concentrated to give a colourless oil. Flash column chromatography (10-35% ethylacetate in hexane) afforded a colourless solid (2.69g, 95%): mp. $64-5^\circ\text{C}$; $[\alpha]_D^{23} -21^\circ$ (c 1.00, CH_2Cl_2); IR (KBr) 3329, 1735, 1702; ^1H NMR (CDCl_3) δ 6.00-5.82 (1H, m), 5.36-5.14 (2H, m), 5.42 (1H, s), 4.56 (1H, d), 4.40-4.08 (2H, m), 4.03 (1H, m), 3.70 (1H, m), 2.52 (2H, m), 1.44 (12H, 2 x s), 1.33 (3H, s); Anal. Calcd for $\text{C}_{16}\text{H}_{27}\text{NO}_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.12; H, 8.16; N, 4.19; MS (+FAB) 320 ($\text{M}^+ + 1$, 41%), 274 (70), 216 (100).

- 634 -

486 ($M^+ + 1$, 33. Accurate mass calculated for $C_{26}H_{32}NO_8$ (MH^+): 486.2128. Found: 486.2121.

(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(5-methyl-3-phenylisoxazoloyloxy)pentanoate (513j), was
 5 synthesized by a similar method as compound 513g to afford a pale orange oil (905mg, 91%): IR (film) 3418, 3383, 2980, 1722, 1711, 1601, 1517, 1450, 1424, 1368, 1308, 1252, 1154, 1100, 994, 767, 698; 1H NMR ($CDCl_3$) δ 7.62-7.55 (2H, m), 7.51-7.42 (3H, m), 5.98-5.76 (1H, m), 5.33-5.18 (2H, m), 4.53 (2H, d), 4.18 (2H, d), 3.91 (1H, m), 3.80 (1H, m), 2.76 (3H, s), 2.50 (2H, m), 1.43 (9H, s). Anal. Calcd for $C_{24}H_{30}N_2O_8 \cdot 0.5H_2O$: C, 59.62; H, 6.46; N, 5.79. Found: C, 59.46; H, 6.24; N, 5.72. MS (ES^+) 497 (100%), 475 ($M^+ + 1$, 15), 419 (48).

15



(3*S*,4*R*) t-Butyl 3-benzylamino-4,5-(dimethylmethylenedioxy)-pentanoate (514), was prepared by the method described in H. Matsunaga, et al.

- 633 -

(1H, d), 5.30-5.13 (2H, m), 4.51 (2H, d), 4.25 (2H, d), 4.18-4.04 (1H, m), 3.88 (1H, m), 3.50 (1H, m), 2.51 (2H, m), 1.41 (9H, s). MS (ES⁺) 508 (57%), 503 (76), 486 (M⁺ + 1, 45), 468 (27), 412 (100). Accurate mass
5 calculated for C₂₆H₃₂NO₈ (MH⁺): 486.2126. Found: 486.2158.

(3S,4R) t-Butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoxyloxy)pentanoate (513h), was prepared from (3S,4R) t-butyl (N-allyloxycarbonyl)-3-amino-4,5-
10 dihydroxypentanoate by the method described for **513g** to afford 562mg (85%) of a colourless oil: IR(film) 3418, 2980, 1722, 1711, 1512, 1368, 1278, 1245, 1198, 1157, 1139; ¹H NMR (CDCl₃) δ 8.90 (1H, d, J = 8.6), 8.21 (1H, dd, J = 1.2, 7.3), 8.04 (1H, d, J = 8.2), 7.89 (1H, dd, J = 1.5, 7.9), 7.67-7.46 (3H, m), 5.88 (1H, m), 5.49
15 (1H, d, J = 9.0), 5.35-5.18 (2H, m), 4.57-4.46 (4H, m), 4.19 (2H, m), 2.67 (2H, m), 1.40 (9H, s). Anal. Calcd for C₂₄H₂₉NO₇: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.74; H, 6.56; N, 3.09. M.S. (ES⁺) 466 (M+Na, 100%),
20 444 (M+1, 39), 388 (44).

(3S,4RS) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(3-henoxybenzoyloxy)pentanoate (513i), was synthesized by a similar method as compound **513g** to afford a
colourless oil (569mg, 85%): IR (film) 3400, 1723,
25 1712, 1584, 1528, 1489, 1443, 1367, 1276, 1232, 1190, 1161, 1098, 1074, 995, 755; ¹H NMR (CDCl₃) δ 8.65-8.59 (1H, d), 7.84-7.66 (2H, m), 7.45-7.11 (5H, m), 7.05-6.97 (2H, m), 6.00-5.78 (1H, m), 5.54-5.14 (2H, m), 4.62-4.52 (2H, m), 4.42-4.32 (2H, m), 4.08-4.22 (2H, m),
30 2.78-2.47 (2H, m), 1.44 (9H, s). MS (ES⁺) 508 (100%),

- 632 -

dd). Anal. Calcd for $C_{15}H_{17}NO_5 \cdot 0.1H_2O$ C, 61.47; H, 5.91; N, 4.78. Found: C, 61.42; H, 5.88; N, 4.81.

(2RS,3R) 3-(Allyloxycarbonylamino)-2-ethoxy-5-oxotetrahydrofuran (513f), was synthesized by a similar method as **513d/e** to afford a colourless oil (152mg, 79%): IR (film) 3334, 2983, 2941, 1783, 1727, 1713, 1547, 1529, 1422, 1378, 1331, 1313, 1164, 1122, 1060, 938; 1H NMR ($CDCl_3$) δ 6.09-5.82 (2H, m), 5.50-5.18 (3H, m), 4.64-4.54 (2H, m), 4.27-4.16 (1H, m), 3.95-3.78 (1H, m), 3.73-3.56 (1H, m), 3.05-2.77 (1H, m), 2.56-2.37 (1H, m), 1.35-1.17 (4H, m). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.16; H, 6.62; N, 5.99. MS (ES^+) 229 ($M^+ + 1$, 100%).

(3S,4RS) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (513g). 4-Dimethylamino-pyridine (76.0mg, 622mmol) was added to a solution of 2-phenoxybenzoyl chloride (579mg, 2.49mmol) and **517** (600mg, 2.07mmol) in pyridine (10ml). The mixture was stirred at room temperature for 18h before adding brine (25ml) and extracting with ethyl acetate (30ml, 20ml). The combined organic extracts were washed with 1M hydrochloric acid (3 x 25ml), saturated aqueous sodium hydrogen carbonate (2 x 25ml) and brine (25ml), dried ($MgSO_4$) and concentrated. The pale orange oil was purified by flash column chromatography (1-10% acetone in dichloromethane) to afford 447mg (44%) of colourless oil: IR (film) 3375, 2980, 1721, 1712, 1602, 1579, 1514, 1484, 1451, 1368, 1294, 1250, 1234, 1161, 1137, 1081, 754; 1H NMR ($CDCl_3$) δ 7.98-7.93 (1H, m), 7.50-7.41 (1H, m), 7.35-7.25 (2H, m), 7.22-7.03 (3H, m), 6.95 (3H, d), 5.95-5.76 (1H, m), 5.57

- 631 -

(1992)]. Following work-up by extraction with ethylacetate and washing with NaHCO_3 , the product was dried (MgSO_4), filtered and evaporated to yield an oil which contained product and benzyl alcohol. Hexane (200ml) (200ml hexane for every 56g of AllocAsp(CO_2tBu) CH_2OH used) was added and the mixture stirred and cooled overnight. This afforded an oily solid. The liquors were decanted and retained for chromatography. The oily residue was dissolved in ethyl acetate and evaporated to afford an oil which was crystallised from 10% ethyl acetate in hexane (~500ml). The solid was filtered to afford **513d** (12.2g, 19%): mp. 108-110°C; $[\alpha]_D^{24} +75.72^\circ$ (c 0.25, CH_2Cl_2); IR (KBr) 3361, 1778, 1720, 1517, 1262, 1236, 1222, 1135, 1121, 944, 930, 760; ^1H NMR (CDCl_3) δ 7.38 (5H, m), 5.90 (1H, m), 5.50 (1H, s), 5.37 (0.5H, m), 5.26 (2.5H, m), 4.87 (1H, ABq), 4.63 (3H, m), 4.31 (1H, m), 3.07 (1H, dd), 2.46 (1H, dd). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.85; H, 5.89; N, 4.80.

The liquors were combined and evaporated to yield an oil (~200g) containing benzyl alcohol. Hexane/ethyl acetate (9:1, 100ml) was added and the product purified by chromatography eluting with 10% ethyl acetate in hexane to remove the excess benzyl alcohol, and then dichloromethane/hexane (1:1 containing 10% ethyl acetate). This afforded **513e** containing some **513d** (20.5g, 32%): mp. 45-48°C; $[\alpha]_D^{24} -71.26^\circ$ (c 0.25, CH_2Cl_2); IR (KBr) 3332, 1804, 1691, 1536, 1279, 1252, 1125, 976. ^1H NMR (CDCl_3) δ 7.38 (5H, m), 5.91 (1H, m), 5.54 (1H, d, $J = 5.2$), 5.38 (3H, m); 4.90 (1H, ABq); 4.60 (4H, m), 2.86 (1H, dd); 2.52 (1H,

- 630 -

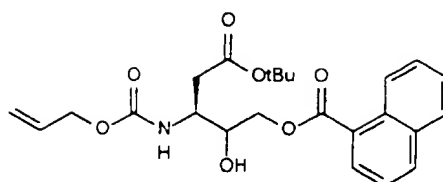
m), 4.59-4.56 (2H, m), 4.32-3.96 (2H, m), 3.85-3.73 (1H, m), 3.02-2.76 (3H, m), 2.49-2.34 (1H, m).

(2R,3S) 3-(Allyloxycarbonyl)amino-2-cyclopentyloxy-5-oxotetrahydrofuran (513b), was prepared as 513d/e to afford 8g (51%) of a mixture of diastereoisomers as a clear oil: $[\alpha]_D^{20} -13^\circ$ (c 0.25, CH₂Cl₂); IR (KBr) 3325, 2959, 2875, 1790, 1723, 1535, 1420, 1328, 1257, 1120, 1049, 973, 937; ¹H NMR (CDCl₃) δ 6.02-5.80 (1H, m), 5.53-5.46 (2H, m), 5.37-5.21 (2H, m), 4.58 (2H, d, J = 5.5), 4.50-4.46 (0.5H, m), 4.34-4.25 (1H, m), 4.19-4.12 (0.5H, m), 3.06-2.77 (1H, m), 2.53-2.35 (1H, m), 1.85-1.50 (8H, m). Anal. Calcd for C₁₃H₁₉NO₅: C, 57.98; H, 7.11; N, 5.20. Found: C, 56.62; H, 7.22; N, 4.95. MS (ES⁺) 270.

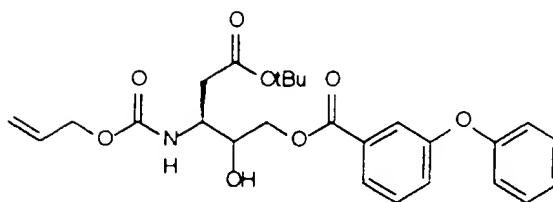
(2R,3S) 3-Allyloxycarbonylamino-2-(indan-2-yloxy)-5-oxotetrahydrofuran (513c), was synthesized by a similar method as compound 513d/e to afford a single isomer (20%) as a pale yellow oil: $[\alpha]_D^{24} -63.1^\circ$ (c 0.2, CH₂Cl₂); IR (film) 3338, 2948, 1791, 1723, 1529, 1421, 1330, 1253, 1122, 984, 929, 746; ¹H NMR (CDCl₃) δ 7.20 (4H, m), 5.87 (1H, m), 5.61 (1H, d, J = 5.4), 5.33-5.10 (2H, m), 4.70 (1H, m), 4.56 (3H, m), 3.33-3.19 (2H, m), 3.10-2.94 (2H, m), 2.81 (1H, dd, J = 8.3, 17.3), 2.43 (1H, dd, J = 10.5, 17.3).

(2R,3S) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydro-furan (513d) and (2S,3S) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxo-tetrahydrofuran (513d/e), were prepared [via method described by Chapman Biorg. & Med. Chem. Lett., 2, pp. 615-618

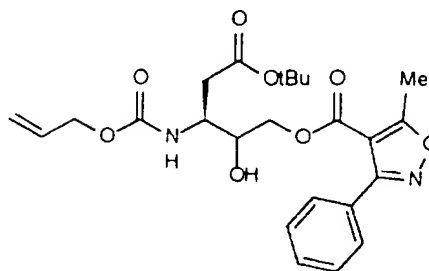
- 629 -



513h




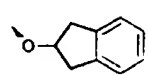
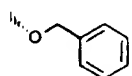
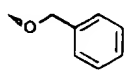



513i



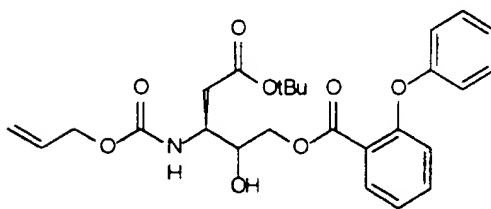
513j

(2*RS*,3*S*) 3-(Allyloxycarbonyl)amino-2-(2-phenethyloxy)-
 5 5-oxotetrahydrofuran (513a), was prepared by a similar
 method as compound 513d/e to afford a mixture of
 diastereoisomers (670mg, 50%) as an oil: IR (KBr) 3331,
 2946, 1790, 1723, 1713, 1531, 1329, 1257, 1164, 1120,
 1060, 977, 937, 701; ¹H NMR (CDCl₃) δ 7.36-7.18 (5H, m),
 10 5.99-5.83 (1H, m), 5.41-5.34 (2H, m), 5.28-5.18 (2H,

- 628 -

513b-2	
513c	
513d	
513e	
513f	
513f-1	
513f-2	

5

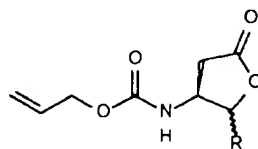


513g

- 627 -

104mg (33%) of a white powder: mp. 115-119°C; $[\alpha]_D^{24}$ -19.8° (c 0.2 MeOH); IR (KBr) 3293, 2944, 1786, 1639, 1578, 1537, 1489, 1450, 1329, 1162, 1124; ^1H NMR (CD₃OD) δ 7.85 (2H, d, J = 7.0), 7.49 (3H, m), 5.49 (1H, m), 4.55 (1H, m), 4.30 (2H, m), 3.40 (1H, m), 3.19-2.89 (3H, m), 2.63 (2H, m), 2.16-1.81 (5H, m), 1.60 (3H, m). Anal. Calcd for C₂₁H₂₆N₄O₆·H₂O: C, 56.24; H, 6.29; N, 12.49. Found: C, 56.54; H, 6.05; N, 12.29. MS (ES⁺) 429 (M - 1, 100%).

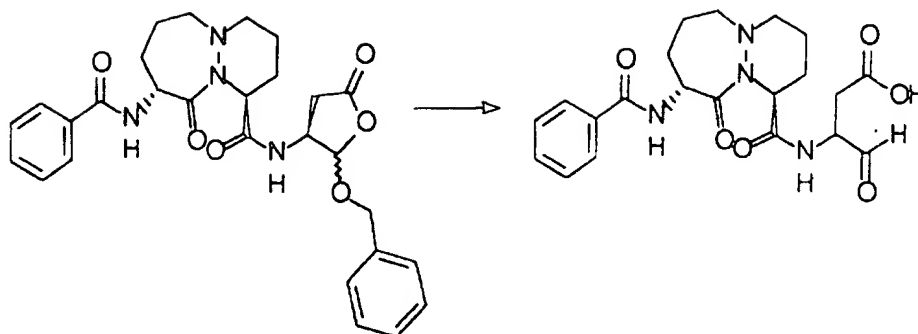
10 Compounds **513a-j** were prepared as described below.

**513a-f**

15

compound	R
513a	
513a-1	
513a-2	
513b	
513b-1	

- 626 -



245b

246b

[1*S*,9*R*(2*RS*,3*S*)] 9-Benzoylamino-*N*-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (245b), was prepared from (1*S*,9*R*) 9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid by the method described for 245 to afford 416mg (85%) of a colourless foam (~1:1 mixture of diastereoisomers): IR (KBr) 3392, 3302, 2942, 1792, 1642, 1529, 1520, 1454, 1119; ¹H NMR (CDCl₃) δ 7.79 (2H, m), 7.51-7.09 (10H, m), 5.52 (0.5H, d, *J* = 5.3), 5.51 (0.5H, s), 5.36 (1H, m), 4.84 (1H, m), 4.74-4.59 (1.5H, m), 4.51 (1H, m), 4.38 (0.5H, m), 3.22-2.83 (5H, m), 2.51 (1H, m), 2.25 (2H, m), 2.01-1.46 (6H, m). Anal. Calcd for C₂₈H₃₂N₄O₆•0.75H₂O: C, 62.97; H, 6.32; N, 10.49. Found: C, 63.10; H, 6.16; N, 10.21. MS (ES⁺) 521 (*M* + 1, 100%).

[3*S*(1*S*,9*R*)] 3-(9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (246b), was prepared from 245b by the method described for 246 to afford

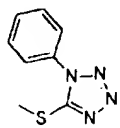
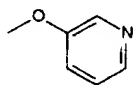
- 625 -

1728, 1659, 1531, 1501, 1415, 1341, 1278, 1253, 1222, 1185; ^1H NMR (CDCl_3) δ 8.05 (1H, d, $J = 7.9$), 7.57 (5H, br s), 5.30 (1H, m), 5.01 (2H, m), 4.70-4.10 (4H, m), 3.40-2.85 (4H, m), 2.62 (1H, m), 2.33 (1H, m), 2.27-
5 1.65 (5H, m), 2.01 (3H, s).

[3S(1S,9S)] t-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoate (512b), was prepared by a
10 similar method as compound 509b, to afford (9%) as a colourless foam: IR (KBr) 3333, 1727, 1661, 1542, 1427, 1369, 1279, 1257, 1232, 1156; ^1H NMR (CDCl_3) δ 8.30 (2H, m), 7.20 (3H, m), 6.45 (1H, d, $J = 7.4$), 5.17 (1H, m), 4.91 (3H, m), 4.55 (1H, m), 3.27 (1H, m), 3.14-2.70
15 (4H, m), 2.41 (1H, m), 2.04 (3H, s), 2.10-1.65 (6H, m), 1.44 (9H, s).

[3S(1S,9S)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoic acid
20 (283d), was prepared by a similar method as compound 280. (100%) as a colourless foam: $[\alpha]_D^{22} -106.0^\circ$ (c 0.2, 10% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$); IR (KBr) 3312, 1735, 1664, 1549, 1426, 1279, 1258, 1200, 1135; ^1H NMR (CDCl_3) δ 8.27 (2H, m), 7.46 (2H, m), 5.09 (1H, m), 4.79 (3H, m), 4.47 (1H, m), 3.40 (1H, m), 3.30-2.70 (3H, m), 2.54 (1H, m), 2.30
25 (1H, m), 1.98 (3H, s), 2.05-1.65 (4H, m).

- 624 -

compound	R
512a 280d	
512b 283d	

5

[3S(1S,9S)] t-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio)pentanoate (512a), was prepared by a similar method as compound 509b, to afford (83%) as a colourless foam: $[\alpha]_D^{23} -129.6^\circ$ (c 0.1, CH₂Cl₂); IR (KBr) 3323, 1726, 1664, 1531, 1501, 1444, 1415, 1394, 1369, 1279, 1254, 1156; ¹H NMR (CDCl₃) δ 7.59 (5H, s), 7.37 (1H, d, J = 7.9), 6.38 (1H, d, J = 7.4), 5.27 (1H, m), 4.98 (2H, m), 4.58 (2H, d + m), 4.28 (1H, d, J = 17.2), 3.28 (1H, m), 3.10-2.65 (4H, m), 2.31 (2H, m), 2.03 (3H, s), 2.10-1.72 (4H, m), 1.48 (9H, s).

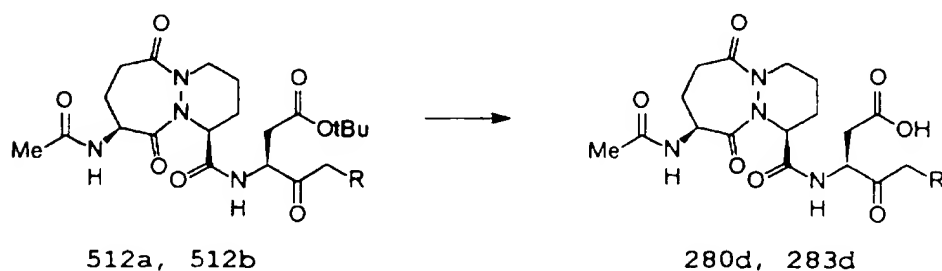
[3S(1S,9S)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio)pentanoic acid (280d), was prepared by a similar method as compound 280, to afford (77%) as a colourless foam: $[\alpha]_D^{22} -93.3^\circ$ (c 0.1, CH₂Cl₂); IR (KBr) 3316,

20

- 623 -

7.20 (2H, s), 5.91 (1H, d), 5.24-5.16 (1H, m), 5.07-4.86 (3H, m), 4.81-4.51 (2H, m), 3.67 (3H, s), 3.34-3.16 (1H, m), 3.10-2.81 (3H, m), 2.72-2.54 (1H, m), 2.41-2.31 (1H, m), 2.07-1.62 (5H, m), 1.47 (9H s). MS (ES⁺) 562 (M⁺ + 1, 100%), 506 (38).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridinyloxy)pentanoic acid (283c), was synthesized by a similar method as compound 280 to afford an off-white powder (167mg, 98%): mp. 90-105°C; (α)_D²² -106° (c 0.11 MeOH); IR (KBr) 3325, 3070, 2956, 1669, 1544, 1423, 1256, 1199, 1133, 1062; ¹H NMR (D₆-DMSO) δ 8.95 (1H, d), 8.45-8.20 (2H, m), 7.53-7.45 (3H, m), 5.19-5.08 (3H, m), 4.70-4.62 (1H, m), 4.41-4.30 (2H, m), 3.53 (3H, s), 2.92-2.68 (3H, m), 2.22-2.06 (2H, m), 1.95-1.82 (2H, m), 1.63-1.53 (1H, m). MS (ES⁺) 506 (M⁺ + 1, 100%).



- 622 -

1688, 1527, 1501, 1458, 1418, 1368, 1279, 1250, 1155, 1064; ^1H NMR (CDCl_3) δ 7.70 (1H, d), 7.63-7.53 (5H, m), 5.84 (1H, d), 5.34-5.27 (1H, m), 5.05-4.92 (1H, m), 4.78-4.54 (3H, m), 4.38 (1H, d), 3.66 (3H, s), 3.37-
5 3.19 (1H, m), 3.07-2.94 (1H, m), 2.91-2.82 (2H, m), 2.71-2.56 (1H, m), 2.40-2.30 (1H, m), 2.19-2.13 (1H, m), 2.08-1.68 (4H, m), 1.42 (9H, s). MS (ES^+) 667 (31%), 645 ($\text{M}^+ + 1$, 100), 589 (62).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-
10 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoic acid (280c), was synthesized by a similar method as compound 280 to afford a pale cream solid (203mg, 88%): mp. 105-130°C;
15 $[\alpha]_{\text{D}}^{22}$ -235° (c 0.11 MeOH); IR (KBr) 3342, 2951, 1727, 1667, 1529, 1501, 1459, 1416, 1276, 1252, 1225, 1192, 1062; ^1H NMR (D_6 -DMSO) δ 8.89 (1H, d), 7.69 (5H, s), 7.50 (1H, d), 5.18-5.11 (1H, m), 4.79-4.69 (1H, m), 4.57 (2H, s), 4.42-4.32 (1H, m), 3.54 (3H, s), 2.92-
20 2.63 (3H, m), 2.21-1.82 (5H, m), 1.65-1.57 (1H, m). MS (ES^+) 587 ($\text{M} - 1$, 100%).

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-
25 (3-pyridinyloxy) pentanoate (508e), was synthesized by a similar method as compound 509b to afford a pale orange solid (199mg, 25%): mp. 80-120°C; $[\alpha]_{\text{D}}^{23}$ -89° (c 0.51 CH_2Cl_2); IR (KBr) 3333, 2978, 1726, 1669, 1578, 1536, 1478, 1426, 1368, 1277, 1253, 1232, 1155, 1064;
30 ^1H NMR (CDCl_3) δ 8.41-8.18 (2H, m), 7.81 (1H, d), 7.26-

- 621 -

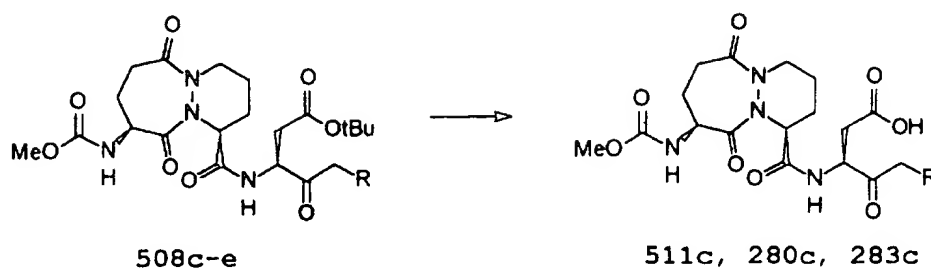
1383, 1253, 1155, 1064; ^1H NMR (CDCl_3) δ 8.49 (2H, d, J = 4.8), 7.13 (1H, d, J = 7.9), 7.03-6.98 (1H, m), 5.47 (1H, d, J = 7.9), 5.23-5.19 (1H, m), 5.09-5.01 (1H, m), 4.84-4.51 (2H, m), 4.04 (2H, AB), 3.69 (3H, s), 3.38-
5 3.19 (1H, m), 3.06-2.64 (4H, m), 2.40-1.76 (6H, m), 1.43 (9H, s). Anal. Calcd for $\text{C}_{25}\text{H}_{34}\text{N}_6\text{O}_8\text{S}$: C, 51.89; H, 5.92; N, 14.52. Found: C, 51.49; H, 6.04; N, 13.87. MS (ES^+) 579.

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methoxycarbonyl)-amino-
10 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(2-mercaptopyrimidine)-4-oxopentanoic acid (511c), was prepared by a similar method as compound 280 to afford 370mg (79%) of a white powder: mp. 105°C (dec); $[\alpha]_{\text{D}}^{22}$
15 -94° (c 0.20, CH_2Cl_2); IR (KBr) 3316, 3057, 2957, 1724, 1664, 1252, 1416, 1384, 1254, 1189, 1063; ^1H NMR (D_6 -DMSO) δ 8.85 (1H, d, J = 7.8), 8.62 (2H, d, J = 4.7), 7.53 (1H, d, J = 8.0), 7.28-7.23 (1H, m), 5.21-5.17 (1H, m), 4.87-4.79 (1H, m), 4.47-4.35 (2H, m), 4.23
20 (2H, AB), 3.58 (3H, s), 3.30-3.21 (1H, m), 2.95-2.50 (4H, m), 2.35-1.60 (6H, m). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_8\text{S} \cdot \text{H}_2\text{O}$: C, 46.66; H, 5.22; N, 15.55. Found: C, 46.66; H, 5.13; N, 15.07. MS (ES^+) 523, (ES^+) 521.

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-
25 (methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoate (508d), was synthesized by a similar method as compound 509b to afford a colourless solid (269mg, 87%): mp. 80-110°C;
30 $[\alpha]_{\text{D}}^{23}$ -108° (c 0.60 CH_2Cl_2); IR (KBr) 3315, 2977, 1727,

- 620 -

5.32 (2H, m), 4.83 (2H, m), 4.45 (2H, m), 3.43-2.77 (4H, m), 2.97 (3H, s), 2.42 (2H, m), 2.05-1.72 (5H, m).



5

10

compound	R
508c 511c	
508d 280c	
508e 283c	

[3*S*(1*S*,9*S*)] *t*-Butyl 3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2-mercaptopyrimidine)-4-oxo-pentanoate (508c), was prepared by a similar method as compound 509b to afford 544mg (97%) of a pale yellow foam: $[\alpha]_D^{20}$ -86° (c 0.19, CH₂Cl₂); IR (KBr) 3426, 2947, 1725, 1669, 1551, 1418,

- 619 -

was prepared by a similar method as compound 280, (100%) as a colourless foam: mp. 120-5°C; $[\alpha]_D^{25}$ -112.4° (c 0.1, CH₂Cl₂); IR (KBr) 3328, 1730, 1664, 1529, 1501, 1410, 1328, 1277, 1219, 1153, 1134, 991; ¹H NMR (CDCl₃) δ 8.07 (1H, d, J = 7.8), 7.58 (5H, s), 6.41 (1H, d, J = 9.5), 5.32 (1H, m), 5.04 (1H, m), 4.70 (1H, d, J = 17.5), 4.60 (3H, m), 3.50-2.9 (3H, m), 2.98 (3H, s), 2.45 (2H, m), 2.06 (4H, m), 1.68 (1H, m).

[3S(1S,9S)] t-Butyl 3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(3-pyridyloxy)pentanoate (504h), was prepared by a similar method as compound 509b (24%) as a colourless foam: $[\alpha]_D^{23}$ -101.0° (c 0.2, CH₂Cl₂); IR (KBr) 3330, 1727, 1669, 1425, 1396, 1369, 1328, 1276, 1256, 1231, 1155, 1137, 991; ¹H NMR (CDCl₃) δ 8.28 (2H, br d, J = 9.4), 7.71 (1H, d, J = 7.9), 7.22 (2H, s), 6.03 (1H, d, J = 9.4), 5.36 (1H, m), 4.95 (2H, m), 4.52 (2H, m), 3.29 (1H, m), 3.07 (3H, s), 3.23-2.75 (3H, m), 2.66-2.35 (2H, m), 2.30-1.60 (5H, m), 1.42 (9H, s).

[3S(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(3-pyridyloxy)pentanoic acid (283b), was prepared by a similar method as compound 280, (100%) as a colourless foam: mp. 120-5°C; $[\alpha]_D^{25}$ -85.2° (c 0.1, 10% CH₃OH/CH₂Cl₂); IR (KBr) 3337, 1738, 1667, 1560, 1457, 1424, 1326, 1317, 1278, 1258, 1200, 1189, 1150, 1133, 991; ¹H NMR (CDCl₃/CD₃OD) δ 8.35 (2H, m), 7.54 (2H, m),

- 618 -

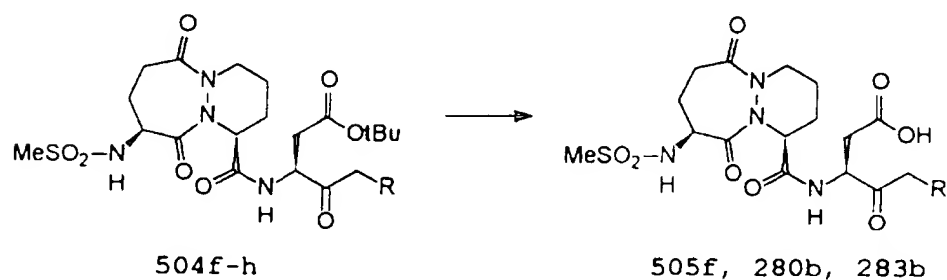
(methylsulphonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid (505f), was prepared by a similar method as compound 508a using 507b and 3-chloro-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one and directly followed by the hydrolysis of 504f with trifluoroacetic to afford a tan powder (65mg, 30%): $[\alpha]_D^{20}$ -128° (c 0.10, MeOH); IR (KBr) 3414, 2928, 1667, 1527, 2459, 1407, 1328, 1274, 1153, 1134; ^1H NMR (MeOD) δ 9.35 (1H, d, J = 6.6H), 8.34 (1H, t, J = 7.2H), 7.99-7.95 (1H, m), 7.76-7.69 (1H, m), 5.85-5.45 (3H, m), 5.30-5.21 (1H, m), 4.93-4.66 (2H, m), 3.81-3.65 (1H, m), 3.66 (3H, m), 3.45-2.52 (4H, m), 2.52-1.71 (6H, m). D.J. Hlasta et al., J. Med. Chem. 1995, 38, 4687-4692.

15 [3S(1S,9S)] t-Butyl 3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoate (504g), was prepared by a similar method as compound 509b, (83%) as a colourless foam: $[\alpha]_D^{23}$ -112.7° (c 0.2, CH_2Cl_2); IR (KBr) 3312, 1726, 1668, 1501, 1413, 1395, 1369, 1328, 1276, 1254, 1155; ^1H NMR (CDCl_3) δ 7.59 (5H, m), 7.48 (1H, d, J = 8.0), 5.68 (1H, d, J = 9.0), 5.37 (1H, m), 4.95 (1H, m), 4.62-4.31 (4H, m), 3.36 (1H, m), 2.98 (3H, s), 2.88 (4H, m), 2.66 (1H, m), 2.42 (2H, m), 1.98 (1H, m), 1.75 (1H, m), 1.43 (9H, s).

[3S(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoic acid (280b),

- 617 -

(1H, d), 7.87 (2H, d), 7.54-7.42 (3H, m), 6.48 (1H, d),
 5.22-5.15 (1H, m), 4.57-4.46 (1H, m), 3.62-3.41 (1H,
 m), 3.22-3.13 (1H, m), 3.02-2.81 (2H, m), 2.70-1.80
 (6H, m). Anal. Calcd for $C_{26}H_{28}N_6O_8 \cdot 1.5H_2O$: C, 54.30;
 5 H, 5.35; N, 14.61. Found: C, 54.14; H, 5.35; N, 13.04.
 MS (ES^+) 551 ($M - 1$, 100%). Accurate mass calculated
 for $C_{26}H_{29}N_6O_8$ (MH^+): 553.2047. Found: 553.2080.



10

compound	R
504f 505f	
504g 280b	
504h 283b	

15 [3*S*(1*S*,9*S*)] 5-(3-Chloro-2-oxy-4*H*-
 pyrido[1,2-*a*]pyrimidin-4-one)-3-[6,10-dioxo-9-

- 616 -

(3-pyridyloxy)pentanoic acid (283), was prepared by a similar method as compound 280 to afford a colourless foam (100%): mp. ~125°C; $[\alpha]_D^{19}$ -84.1° (c 0.1, 20% MeOH/CH₂Cl₂); IR (KBr) 3401, 1736, 1663, 1538, 1489, 5 1459, 1425, 1281, 1258, 1200, 1134; ¹H NMR (CD₃OD/CDCl₃) δ 8.38 (2H, m), 7.84-7.40 (8H, m), 5.16 (4H, m), 4.80 (1H, m), 4.56 (1H, m), 3.50 (1H, m), 3.12 (2H, m), 2.82 (2H, m), 2.37 (1H, m), 2.10-1.65 (5H, m). Anal. Calcd for C₂₇H₂₉N₅O₈•0.4H₂O: C, 51.77; H, 4.61; N, 10.41. 10 Found: C, 52.19; H, 4.93; N, 9.99.

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenylcarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(2-[4(3H)-pyrimidone])pentanoate (509d), was 15 synthesized by a similar method as compound 509b to afford a colourless solid (49.6mg, 82%): ¹H NMR (CDCl₃) δ 8.02 (1H, s), 7.95-7.86 (1H, m), 7.84-7.76 (2H, m), 7.62-7.35 (4H, m), 7.22-7.07 (1H, m), 6.43 (1H, d), 5.26-5.08 (2H, m), 5.03-4.72 (3H, m), 4.66-4.50 (1H, 20 m), 3.43-3.19 (1H, m), 3.15-2.97 (1H, m), 2.86-2.72 (3H, m), 2.48-2.31 (1H, m), 2.18-1.60 (6H, m), 1.43 (9H, s).

[3S(1S,9S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenylcarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(2-[4(3H)-pyrimidone])pentanoic acid (510d), was 25 synthesized by a similar method as compound 280 to afford a colourless solid (25.7mg, 57%): mp. 140-80°C; IR (KBr) 3391, 2945, 1733, 1664, 1530, 1422, 1363, 30 1277, 1259, 1204; ¹H NMR (CD₃OD) δ 8.23 (1H, s), 7.94

- 615 -

room temperature for 30min before evaporation under reduced pressure. The residue was triturated with dry toluene and evaporated. Chromatography on silica gel eluting with 10% methanol in dichloromethane gave a
5 colourless glass which was crystallised from dichloromethane/diethyl ether to give 62mg (69%) of colourless solid: mp. 145°C (decomp.); $[\alpha]_D^{22}$ -80.9° (c 0.1, CH₂Cl₂); IR (KBr) 3400, 1727, 1658, 1530, 1501, 1460, 1445, 1416, 1280, 1254; ¹H NMR (CDCl₃) δ 8.00 (1H,
10 m), 7.79 (2H, d, J = 6.7), 7.58-7.30 (9H, m), 5.25 (2H, m), 4.94 (1H, m), 4.53 (2H, m), 4.35 (1H, m), 3.35 (1H, m), 3.01 (3H, m), 2.73 (1H, m), 2.38 (1H, m), 1.98 (4H, m), 1.64 (1H, m). Anal. Calcd for C₂₉H₃₀N₈O₇S•0.2TFA: C, 53.71; H, 4.63; N, 17.04. Found: C, 53.97; H, 4.92; N, 15 16.77. MS (ES⁺) 633.55 (M⁺ - 1).

[3S(1S,9S)] t-Butyl 3-[9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridyloxy)pentanoate (509c), was prepared by a
20 similar method as compound 509b to afford a colourless glass (34%): $[\alpha]_D^{22}$ -77.1° (c 0.25, CH₂Cl₂); IR (film) 3311, 1724, 1658, 1603, 1578, 1536, 1488, 1458, 1426, 1368, 1340, 1279, 1256, 1231, 1155, 707; ¹H NMR (CDCl₃) δ 8.29 (2H, m), 7.84 (2H, m), 7.48 (4H, m), 7.22 (3H,
25 m), 5.20 (2H, m), 4.90 (2H, m), 4.58 (1H, m), 3.29 (1H, m), 3.20-2.70 (4H, m), 2.38 (2H, m), 1.96 (4H, m), 1.68 (1H, m), 1.42 (9H, s). MS (ES⁺) 608.54 (M + 1).

[3S(1S,9S)] 3-[9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-
30

- 614 -

Calcd for $C_{25}H_{27}N_5O_4S_2 \cdot H_2O$: C, 50.75; H, 4.94 N, 11.84.
Found: C, 51.34; H, 4.70; N, 11.58. MS (ES^+) 572.

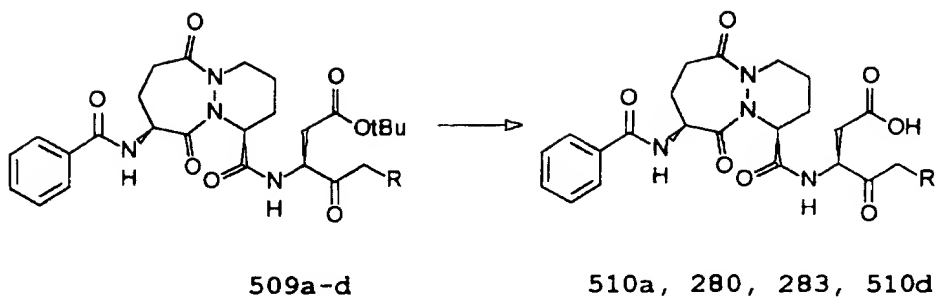
- [3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-
5 pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-
(1-phenyl-1H-tetrazole-5-thio) pentanoate (509b). 507a
(100mg, 0.17mmol) in dry dimethylformamide (1.5ml) was
treated with 1-phenyl-1H-tetrazole-5-thiol (33mg,
0.187mmol) and potassium fluoride (15mg, 0.34mmol).
10 The mixture was stirred at room temperature for 2h,
diluted with ethyl acetate, washed with aqueous sodium
bicarbonate (x2), brine, dried ($MgSO_4$) and evaporated.
The product was purified by flash chromatography on
silica gel eluting with ethyl acetate to give 103mg
15 (88%) as a colourless foam: $[\alpha]_D^{23} -92.2^\circ$ (c 0.1,
 CH_2Cl_2); IR (KBr) 3334, 1726, 1660, 1528, 1501, 1417,
1394, 1368, 1279, 1253, 1155; 1H NMR ($CDCl_3$) δ 7.82 (2H,
m), 7.60-7.40 (8H, m), 7.39 (1H, d, J = 8.1), 7.05 (1H,
d, J = 7.3), 5.26 (1H, m), 5.15 (1H, m), 4.99 (1H, m),
20 4.60 (2H, m), 4.30 (1H, d, J = 17.2H), 3.32 (1H, m),
3.10-2.75 (4H, m), 2.40 (1H, m), 2.24 (1H, m), 1.90
(3H, m), 1.75 (1H, m), 1.44 (9H, s). MS (ES^+) 691.47
($M^+ + 1$).

- [3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-
25 1,2,3,4,7,8,9,10-octahydro-6H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-
5(1-phenyl-1H-tetrazole-5-thio) pentanoic acid (280),
was synthesized via method used to prepare 505 from
504. 509b (98mg, 0.142mmol) in dichloromethane (1ml)
30 was cooled to 0° and trifluoroacetic acid (1ml) was
added. The mixture was stirred at 0° for 15min and at

- 613 -

acid in acetic acid (1.84ml, 9.2mmol, 2.2equiv) at 0°C, under nitrogen. After 10min stirring at 0°C the reaction was complete and a white solid crystallised in the medium. The solid was filtered and washed with ethylacetate and diethylether to afford 2.20g (100%) of [3S(1S,9S)] 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid which was used without further purification: ¹H NMR (D₆-DMSO) δ 8.87 (1H, d, J = 7.3), 8.63 (1H, d, J = 7.6), 7.91-7.87 (2H, m), 7.60-7.44 (3H, m), 6.92 (1H, bs), 5.14-5.09 (1H, m), 4.92-4.65 (2H, m), 4.43 (2H, AB), 4.41-4.35 (1H, m), 3.33-3.22 (1H, m), 2.98-2.90 (1H, m), 2.89-2.57 (2H, m), 2.35-2.15 (3H, m), 1.99-1.91 (2H, m), 1.75-1.60 (2H, m). A solution of the bromoketone (535mg, 1mmol) in dry DMF (10ml) was treated with potassium fluoride (150mg, 2.5mmol, 2.5 equiv), under nitrogen. After 5min stirring at room temperature, 2-mercaptothiazole (140mg, 1.2mmol, 1.2equiv) was added. After overnight reaction ethylacetate (150ml) was added and the organic solution was washed with brine, dried over magnesium sulphate and reduced in vacuo. The residue was crystallised in diethyl ether, filtered and purified on silica gel using a gradient of MeOH (0% to 5%) in dichloromethane. Evaporation afforded 344mg (60%) of a white solid: mp. 90-95°C (decomp.); [α]_D²⁰ -82° (c 0.2, CH₂Cl₂); IR (KBr) 3328, 2941, 1745, 1659, 1535, 1422, 1276, 1255, 1223, 1072; ¹H NMR (D₆-DMSO) δ 8.92 (1H, d, J = 7.6), 8.68 (1H, d, J = 7.6), 7.98-7.90 (2H, m), 7.75-7.67 (1H, m), 7.64-7.50 (4H, m), 5.22-5.18 (1H, m), 4.95-4.74 (2H, m), 4.58-4.38 (3H, m), 3.52-3.19 (1H, m), 3.05-2.65 (4H, m), 2.40-1.50 (6H, m). Anal.

- 612 -



compound	R
509a 510a	
509b 280	
509c 283	
509d 510d	

[3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2-mercaptothiazole)-4-oxopentanoic acid (510a). A

15 solution of 506a (2.27g, 4.2mmol) in dry dichloromethane (50ml) was treated with 30% hydrobromic

- 611 -

m). Anal. Calcd for $C_{24}H_{26}N_4O_{10} \cdot H_2O$: C, 46.54; H, 4.56; N, 9.05. Found: C, 46.36; H, 4.14; N, 8.88.

[3S(1S,9S)] t-Butyl 5-(2,6-dimethylbenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (508b), was synthesized by a similar method as compound 508a to afford a pale yellow foam (460mg, 82%): $[\alpha]_D^{22} -115^\circ$ (c 0.20, CH_2Cl_2); IR (KBr) 3413, 2960, 1729, 1675, 1528, 1514, 1461, 1421, 1368, 1265, 1116, 1096; 1H NMR ($CDCl_3$) δ 7.27-7.03 (4H, m), 5.48 (1H, d, $J = 8.2$), 5.20-5.14 (1H, m), 5.04 (2H, AB), 4.93-4.86 (1H, m), 4.80-4.56 (2H, m), 3.77 (3H, s), 3.32-3.15 (1H, m), 3.00-2.56 (4H, m), 2.37 (6H, s), 2.19-1.77 (5H, m), 1.45 (9H, s), 2.41-2.25 (1H, m). MS (ES^+) 617.

[3S(1S,9S)] 5-(2,6-Dimethylbenzoyloxy)3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (285), was synthesized by a similar method as compound 284 to afford a white solid (303mg, 78%): mp. $110^\circ C$ (decomp.); $[\alpha]_D^{20} -128^\circ$ (c 0.10, CH_2Cl_2); IR (KBr) 3339, 2958, 1731, 1666, 1529, 1420, 1266, 1248, 1115, 1070; 1H NMR (D_6 -DMSO) δ 8.90 (1H, d, $J = 7.4$), 7.54 (1H, d, $J = 7.9$), 7.36-7.28 (1H, m), 7.17-7.14 (2H, m), 5.19-5.15 (3H, m), 4.84-4.74 (1H, m), 4.45-4.37 (2H, m), 3.59 (3H, s), 3.45-3.25 (1H, m), 2.95-2.64 (4H, m), 2.35 (6H, s), 2.30-1.60 (6H, m). Anal. Calcd for $C_{26}H_{32}N_4O_{10} \cdot H_2O$: C, 53.98; H, 5.92; N, 9.68. Found: C, 53.50; H, 5.52; N, 9.49. MS (ES^+) 559.

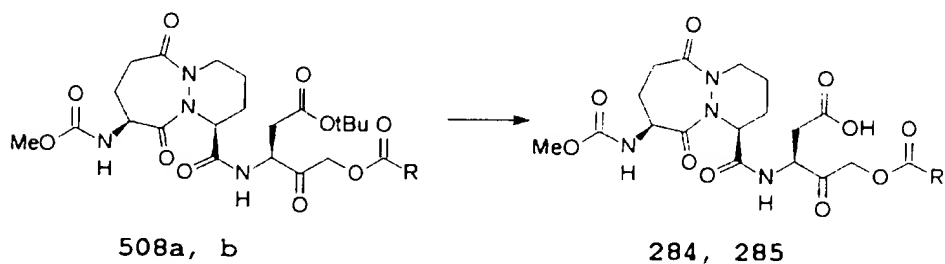
- 610 -

506c (547mg, 1mmol) in DMF (4ml) was added potassium fluoride (145mg, 2.5mmol, 2.5 equiv). After 10min stirring at room temperature, 2,6-dichlorobenzoic acid (229mg, 1.2mmol, 1.2 equiv) was added. After 3h
5 reaction at room temperature, ethyl acetate (30ml) was added. The solution was washed with a saturated solution of sodium bicarbonate (30ml), brine, dried over MgSO₄ and concentrated in vacuo to afford 590mg (90%) of a pale yellow foam: $[\alpha]_D^{22} -85^\circ$ (c 0.20, CH₂Cl₂); IR (KBr) 3400, 2956, 1737, 1675, 1528, 1434, 1414, 1368, 1344, 1272, 1197, 1152, 1061; ¹H NMR (CDCl₃) δ 7.36-7.33 (3H, m), 7.04 (1H, d, J = 8.0), 5.46 (1H, d, J = 7.8), 5.19-5.16 (1H, m), 5.08 (2H, AB), 4.97 - 4.55 (1H, m), 4.69-4.55 (2H, m), 3.68 (3H, s),
10 3.30-3.10 (1H, m), 3.01-2.50 (4H, m), 2.40-2.33 (1H, m), 2.15-1.60 (5H, m), 1.44 (9H, s). Anal. Calcd for C₂₈H₃₄Cl₂N₄O₁₀: C, 51.15; H, 5.21; N, 8.52. Found: C, 51.35; H, 5.32; N, 8.56.

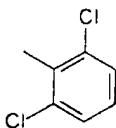
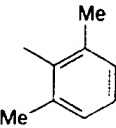
[3S(1S,9S)] 5-(2,6-Dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (284), was synthesized from **508a** via method used to prepare **505** from **504** which afforded 330mg (65%) of a white solid: mp. 115°C (decomp.);
25 $[\alpha]_D^{20} -107^\circ$ (c 0.2, CH₂Cl₂); IR (KBr) 3340, 2954, 1738, 1664, 1530, 1434, 1272, 1198, 1148, 1060; ¹H NMR (D₆-DMSO) δ 8.91 (1H, d, J = 7.2H), 7.67-7.63 (3H, m), 7.54 (1H, d, J = 8.0), 5.24 (2H, s), 5.20-5.15 (1H, m), 4.79-4.70 (1H, m), 4.46-4.37 (2H, m), 3.58 (3H, s),
30 3.33-3.20 (1H, m), 2.94-2.55 (4H, m), 2.30-1.60 (6H,

- 609 -

method as compound **507a** to afford a pale yellow foam (84%): $[\alpha]_D^{22}$ -109.6° (c 0.1, CH₂Cl₂); IR (KBr) 3324, 1727, 1659, 1535, 1458, 1444, 1423, 1369, 1279, 1256, 1223, 1155; ¹H NMR (CDCl₃) δ 7.12 (1H, d, J = 7.8), 6.33 (1H, d, J = 7.5), 5.19 (1H, m), 4.97 (2H, m), 4.58 (1H, m), 4.06 (2H, s), 3.20 (1H, m), 3.05-2.69 (4H, m), 2.35 (1H, m), 2.14-1.68 (5H, m), 2.03 (3H, s), 1.44 (9H, s). Anal. Calcd for C₂₁H₃₁BrN₄O₇•0.3H₂O: C, 46.99; H, 5.93; N, 10.44. Found: C, 46.97; H, 5.90; N, 10.35.



10

compound	R
508a 284	
508b 285	

15 **[3S(1S,9S)] t-Butyl 5-(2,6-dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoate (508a)**. To a solution of

- 608 -

[3S(1S,9S)] t-Butyl 5-bromo-3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507b), was prepared by a similar method as compound 507a. (68%) as an orange foam: $[\alpha]_D^{20}$ -135° (c 0.053, CH₂Cl₂); IR (KBr) 3429, 2944, 2935, 1723, 1670, 1458, 1408, 1327, 1225, 1154, 991; ¹H NMR (CDCl₃) δ 7.38 (1H, d, J = 8.2), 5.69 (1H, d, J = 9.3), 5.43-5.34 (1H, m), 5.07-4.97 (1H, m), 4.70-4.42 (2H, m), 4.12 (2H, s), 3.35-3.17 (1H, m), 3.10-2.69 (4H, m), 2.98 (3H, s), 2.43-2.33 (1H, m), 2.15-1.65 (5H, m), 1.43 (9H, s). Anal. Calcd for C₂₀H₃₁BrN₄O₈S: C, 42.33; H, 5.51; N, 9.87. Found: C, 42.69; H, 5.52; N, 9.97.

[3S(1S,9S)] t-Butyl 5-bromo-3-(6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507c), was prepared by a similar method as compound 507a to afford a pale yellow foam (320mg, 78%): $[\alpha]_D^{20}$ -107° (c 0.2, CH₂Cl₂); IR (KBr) 3401, 2956, 1726, 1670, 1528, 1452, 1415, 1395, 1368, 1276, 1251, 1155, 1064; ¹H NMR (CDCl₃) δ 7.07 (1H, d, J = 7.6), 5.47 (1H, d, J = 8.1), 5.21-5.16 (1H, m), 5.03-4.94 (1H, m), 4.75-4.56 (2H, m), 4.06 (2H, s), 3.69 (3H, s), 3.31-3.13 (1H, m), 3.03-2.92 (2H, m), 2.81-2.58 (2H, m), 2.41-2.31 (1H, m), 2.10-1.66 (5H, m), 1.44 (9H, s).

[3S(1S,9S)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-bromo-4-oxopentanoate (507g), was prepared by a similar

- 607 -

method as compound **506a**. 81%: $[\alpha]_D^{28} -146.7^\circ$ (c 0.4, CH₂Cl₂); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155; ¹H NMR (CDCl₃) δ 7.32 (1H, d), 6.43 (1H, d), 5.50 (1H, s), 5.22 (1H, m), 4.94 (1H, m), 4.77 (1H, m), 4.60 (1H, m), 3.24 (1H, m), 3.03-2.52 (4H, m), 2.36 (1H, m), 2.10-1.64 (5H, m), 2.02 (3H, s), 1.45 (9H, s). Anal. Calcd for C₂₁H₂₀N₆O₇: C, 52.69; H, 6.32; N, 17.05. Found: C, 52.51; H, 6.27; N, 17.36. MS (ES⁺) 477 (M⁺ - 1, 100%).

- 10 **[3S(1S,9S)] t-Butyl 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507a)**. **506a** (3.0g, 5.55mmol) in dry dichloromethane (40ml) was cooled to 0° and 30% hydrobromic acid in acetic acid (1.1ml, 5.55mmol) was added dropwise over 4min. The mixture was stirred at 0° for 9min and quenched with aqueous sodium bicarbonate. The product was extracted into ethyl acetate, washed with aqueous sodium bicarbonate, brine, dried (MgSO₄) and evaporated to give 2.97g (92%) of a colourless foam: $[\alpha]_D^{23} -82.3^\circ$ (c 0.23, CH₂Cl₂); IR (KBr) 3333, 1726, 1659, 1530, 1458, 1447, 1422, 1395, 1368, 1279, 1256, 1222, 1155, 728; ¹H NMR (CDCl₃) δ 7.81 (2H, m), 7.50 (3H, m), 7.11 (1H, d, J = 8.0), 7.01 (1H, d, J = 7.4), 5.20 (2H, m), 5.00 (1H, m), 4.06 (2H, s), 3.28 (1H, m), 3.20-2.70 (4H, m), 2.42 (1H, m), 2.10-1.85 (4H, m), 1.72 (1H, m), 1.44 (9H, s). Anal. Calcd for C₂₆H₃₃N₄O₇Br·0.7H₂O: C, 51.53; H, 5.72; N, 9.24. Found: C, 51.55; H, 5.52; N, 9.09. MS (ES⁺) 595, 593 (M⁺ + 1).

- 606 -

1.85 (4H, m), 1.70 (1H, m), 1.45 (9H, s). MS (ES^+)
539.58 (M - 1, 97.9%) 529.59 (100).

[3S(1S,9S)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methanesulphonamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506b), was prepared by a similar method as compound 506a. 74% as yellow orange solid: mp. 75°C (decomp.); $[\alpha]_D^{20}$ -92.0° (c 0.036, CH₂Cl₂); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155; ¹H NMR (CDCl₃) δ 7.48 (1H, d, J = 8.1), 5.83-5.68 (1H, m), 5.55-5.50 (1H, m), 5.43-5.14 (1H, m), 4.83-4.45 (3H, m), 3.40-3.19 (1H, m), 2.98 (3H, s), 2.92-2.30 (4H, m), 2.24-1.70 (6H, m), 1.43 (9H, s).

[3S(1S,9S)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506c), was prepared by a similar method as compound 506a to afford a pale yellow foam (405mg, 82%): $[\alpha]_D^{20}$ -144° (c 0.2, CH₂Cl₂); IR (KBr) 3339, 2978, 2958, 2112, 1728, 1674, 1530, 1459, 1415, 1367, 1274, 1252, 1154, 1063; ¹H NMR (CDCl₃) δ 7.23 (1H, d, J = 8.2), 5.51-5.31 (2H, m), 5.21-5.16 (1H, m), 4.77-4.55 (3H, m), 3.68 (3H, s), 3.35-3.18 (1H, m), 3.04-2.51 (4H, m), 2.40-2.30 (1H, m), 2.09-1.66 (5H, m), 1.45 (9H, s). MS (ES^+) 493.

[3S(1S,9S)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-diazo-4-oxopentanoate (506g), was prepared by a similar

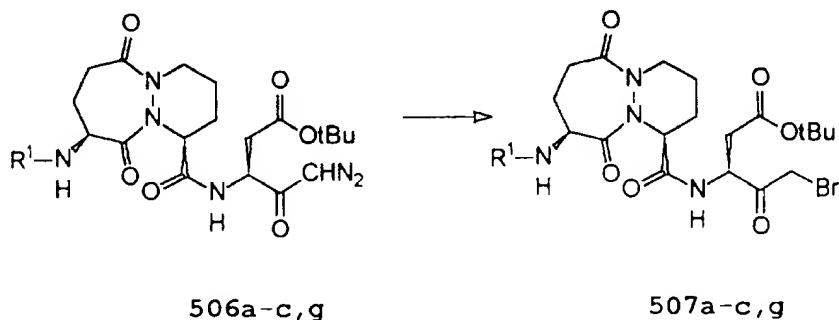
- 605 -

compound	R ¹
506a 507a	PhC(O)-
506b 507b	MeS(O) ₂ -
506c 507c	MeOC(O)-
506g 507g	CH ₃ C(O)-

- 5
- 10 [3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-diazo-
4-oxopentanoate (506a). A solution of 212e (321mg,
0.929mmol) and (3S) t-butyl 3-amino-5-diazo-4-
15 oxopentanoate (198mg, 0.929mmol) in dichloromethane
(3ml) was cooled to 0° and N,N-diisopropylethylamine
(0.16ml, 1.86mmol) and [2-(1H-benzotriazol-1-yl)-
1,1,3,3-tetramethyl-uronium tetrafluoroborate (328mg,
1.02mmol) were added. The solution was stirred
20 overnight at room temperature, diluted with ethyl
acetate and washed with 1M NaHSO₄ (x2), aqueous NaHCO₃
(x2), brine, dried over magnesium sulphate and
evaporated. Chromatography on silica gel eluting with
ethyl acetate gave 506a (425mg, 85%) as a colourless
25 foam: $[\alpha]_D^{23}$ -124.9° (c 0.2, CH₂Cl₂); IR (KBr) 3332,
2111, 1728, 1658, 1532, 1421, 1392, 1367, 1279, 1256,
1155; ¹H NMR (CDCl₃) δ 7.82 (2H, m), 7.49 (3H, m), 7.28
(1H, d, J = 9.3), 7.05 (1H, d, J = 7.3), 5.06 (1H, s),
5.18 (2H, m), 4.78 (1H, m), 4.62 (1H, m), 3.29 (1H, m),
30 3.08-2.79 (3H, m), 2.58 (1H, dd, J = 16.8, 5.6), 2.20-

- 604 -

[3S(1S,9S)] 5-(3-Chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid (505e). A solution of 217 (0.33g, 0.51mmol) in dry dichloromethane (3ml) was cooled (ice/water) with protection from moisture. Trifluoroacetic acid (2ml) was added with stirring. The solution was kept at room temperature for 2h after removal of the cooling bath, then concentrated in vacuo. The residue was evaporated three times from dichloromethane, triturated with diethyl ether and filtered. The solid was purified by flash chromatography (silica gel, 0-6% methanol in dichloromethane) to give the product as a white glassy solid (0.296g, 98%): mp 110-122°C; $[\alpha]_D^{22}$ -163.5° (c 0.1, CH₃OH); IR (KBr) 3514-3337, 1726, 1664, 1513, 1420, 1245, 1152, 1134, 990; ¹H NMR (CD₃OD) δ 7.79 (1H, d, J = 5.2), 7.12 (1H, d, J = 5.2), 5.20 (1H, m), 5.02-4.72 (2H, m, masked by H₂O), 4.59-4.32 (3H, m), 3.48-3.29, 3.08-2.75, 2.50-2.41, 2.31-2.22, 2.08-1.89, 1.72-1.63 (11H, 6m), 2.95 (3H, s).



- 603 -

2.19-2.06 (2H, m), 2.02-1.79 (3H, m), 1.63-1.52 (1H, m). Anal. Calcd for $C_{29}H_{32}N_4O_{11}S \cdot 0.5H_2O$: C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.24; H, 5.14; N, 8.34; S, 4.86. MS (ES^+) 643 (M - 1, 100%), 385 (62).

- 5 [3S,4R(1S,9S)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxypentanoate (503e), was prepared by a similar method to that described for compound
- 10 213e, to afford an off white solid (70%): mp. 100-103°C; $[\alpha]_D^{25}$ -84.0° (c 0.05, CH_2Cl_2); IR (KBr) 3459-3359, 1722, 1664, 1514, 1368, 1328, 1278, 1247, 1155; 1H NMR ($CDCl_3$) δ 7.52 (1H, m), 7.06-6.99 (2H, m), 5.69 (1H, d, J = 9.0), 5.23 (1H, m), 4.61-4.16 (6H, m),
- 15 3.36-3.19 (1H, m), 2.96 (3H, s), 2.67-2.49, 2.42-2.32, 2.06-1.89, 1.69 (10H, 4m), 1.43 (9H, s).

- [3S(1S,9S)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-
- 20 carboxamido)-4-oxopentanoate (504e), was prepared by a similar method to that described for compound 216e, to afford a white solid (98%): mp. 91-98°C; $[\alpha]_D^{25}$ -112.5° (c 0.06, CH_2Cl_2); IR (KBr) 3453-3364, 1727, 1668, 1513, 1420, 1368, 1245, 1155; 1H NMR ($CDCl_3$) δ 7.54
- 25 (1H, d, J = 5.3), 7.18 (1H, d, J = 7.18), 7.05 (1H, d, J = 5.4), 5.42 (1H, d, J = 8.9), 5.25 (1H, m), 5.02 (2H, m), 4.96-4.87 (1H, m), 4.65-4.42 (2H, m), 3.34-3.17 (1H, m), 2.97-2.93 (1H, m), 2.97 (3H, s), 2.87-2.78, 2.73-2.50, 2.38-2.32, 2.13-1.88, 1.69-1.60 (9H,
- 30 5m), 1.44 (9H, s).

- 602 -

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy) pentanoate (504d), was

5 synthesized by a similar method as compound 216e to afford a colourless powder (466mg, 85%): mp. 75-100°C; $[\alpha]_D^{22}$ -99.3° (c 0.60, CH₂Cl₂); IR (KBr) 3335, 2978, 2937, 1728, 1669, 1584, 1525, 1487, 1444, 1416, 1369, 1328, 1272, 1227, 1188, 1155, 989, 754; ¹H NMR (CDCl₃) δ
10 7.82-7.77 (1H, m), 7.66-7.65 (1H, m), 7.46-7.32 (4H, m), 7.26-7.10 (2H, m), 7.04-6.98 (2H, m), 5.68 (1H, d), 5.37-5.31 (1H, m), 5.11 (1H, d), 5.02-4.88 (2H, m), 4.66-4.42 (2H, m), 3.35-3.17 (1H, m), 2.98-2.89 (1H, m), 2.96 (3H, s), 2.84-2.78 (1H, m), 2.72-2.47 (1H, m),
15 2.42-2.32 (1H, m), 2.14-1.58 (6H, m), 1.43 (9H, s).
Anal. Calcd for C₃₃H₄₀N₄O₁₁S: C, 56.56; H, 5.75; N, 8.00. Found: C, 56.36; H, 5.82; N, 7.71. MS (ES⁺) 723 (56%), 718 (90), 701 (M⁺ + 1, 36), 645 (100).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-
20 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy)pentanoic acid (505d), was
synthesized by a similar method as compound 217 to afford a colourless foam (353mg, 73%): mp. 80-115°C;
25 $[\alpha]_D^{23}$ -138° (c 0.11, MeOH); IR (KBr) 3327, 2937, 1728, 1666, 1584, 1529, 1487, 1443, 1413, 1328, 1273, 1227, 1189, 1155, 1134, 989, 754; ¹H NMR (D₆-DMSO) δ 8.82 (1H, d), 7.76-7.72 (1H, m), 7.61-7.53 (2H, m), 7.48-7.32 (4H, m), 7.24-7.17 (1H, m), 7.11-7.06 (2H, m),
30 5.14-5.06 (3H, m), 4.73-4.64 (1H, m), 4.38-4.24 (2H, m), 2.92 (3H, s), 2.89-2.61 (3H, m), 2.38-2.27 (1H, m),

- 601 -

- (2-phenoxybenzoyloxy)pentanoic acid (505c), was synthesized by a similar method as compound 217 to afford a colourless foam (252mg, 72%): mp. 90-125°C; $[\alpha]_D^{23}$ -133° (c 0.11, MeOH); IR (KBr) 3314, 2938, 1792, 1734, 1663, 1604, 1535, 1483, 1448, 1415, 1250, 1132, 756; ^1H NMR (D_6 -DMSO) δ 8.81-8.76 (1H, m), 7.92 (1H, d), 7.68-7.54 (2H, m), 7.41-7.25 (3H, m), 7.16-6.91 (4H, m), 5.13-4.98 (2H, m), 4.72-4.63 (1H, m), 4.37-4.21 (2H, m), 2.92 (3H, s), 2.90-2.60 (3H, m), 2.35-2.26 (1H, m), 2.17-2.05 (2H, m), 1.99-1.80 (2H, m), 1.61-1.50 (1H, m). Anal. Calcd for $\text{C}_{29}\text{H}_{32}\text{N}_4\text{O}_{11}\text{S} \cdot 0.5\text{H}_2\text{O}$: C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.57; H, 5.18; N, 8.32; S, 4.75. MS (ES^+) 643 (M - 1, 100%).
- 15 [3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-hydroxy-5-(3-phenoxybenzoyloxy) pentanoate (503d), was synthesized by a similar method as compound 213e to afford a colourless solid (563mg, 90%): IR (KBr) 3349, 2978, 2935, 1724, 1664, 1583, 1536, 1489, 1443, 1370, 1327, 1271, 1226, 1189, 1155, 1073, 990, 755; ^1H NMR (CDCl_3) δ 7.77 (1H, d), 7.67 (1H, m), 7.45-7.10 (6H, m), 7.00 (2H, d), 5.93-5.80 (1H, m), 5.36-5.30 (1H, m), 4.63-4.24 (5H, m), 4.15-4.09 (1H, m), 3.37-3.22 (1H, m), 2.98-2.74 (1H, m), 2.94 (3H, s), 2.70-2.47 (3H, m), 2.40-2.30 (1H, m), 2.15-1.60 (5H, m), 1.42 (9H, s). Anal. Calcd for $\text{C}_{33}\text{H}_{42}\text{N}_4\text{O}_{11}\text{S} \cdot \text{H}_2\text{O}$: C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.60; H, 5.88; N, 7.49; S, 4.50. MS (ES^+) 725 (19%), 720 (91), 703 ($\text{M}^+ + 1$, 74), 647 (76), 629 (100), 433 (78).

- 600 -

(1H, m), 7.39-7.18 (3H, m), 7.14-7.07 (1H, m), 7.00-6.90 (3H, m), 6.75 (1H, d), 5.57-5.50 (1H, m), 5.21-5.09 (1H, m), 4.64-4.42 (2H, m), 4.36-4.12 (3H, m), 3.95-3.87 (1H, m), 3.39-3.18 (1H, m), 3.00-2.82 (1H, m), 2.95 (3H, s), 2.69-2.48 (3H, m), 2.42-2.28 (1H, m), 2.07-1.62 (6H, m), 1.42 (9H, s). Anal. Calcd for $C_{33}H_{42}N_4O_{11}S \cdot H_2O$: C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.95; H, 5.95; N, 7.34; S, 4.20. MS (ES^+) 725 (26%), 720 (47), 703 ($M^+ + 1$, 34), 433 (100), 403 (89).

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(2-phenoxybenzoyloxy) pentanoate (504c), was synthesized by a similar method as compound **216e** to afford a colourless powder: mp. 85-100°C; $[\alpha]_D^{22} -91.3^\circ$ (c 0.52, CH_2Cl_2); IR (KBr) 3328, 2978, 2935, 1732, 1669, 1603, 1524, 1483, 1450, 1396, 1369, 1296, 1276, 1237, 1155, 1132, 1082, 989, 755; 1H NMR ($CDCl_3$) δ 8.03-7.98 (1H, m), 7.52-7.44 (1H, m), 7.37-7.07 (5H, m), 7.01-6.92 (3H, m), 5.52 (1H, d), 5.28-5.20 (1H, m), 5.06-4.84 (3H, m), 4.64-4.39 (2H, m), 3.32-3.14 (1H, m), 2.99-2.88 (1H, m), 2.94 (3H, s), 2.65-2.45 (2H, m), 2.39-2.29 (1H, m), 2.12-1.58 (6H, m), 1.40 (9H, s). Anal. Calcd for $C_{33}H_{40}N_4O_{11}S$: C, 56.56; H, 5.75; N, 8.00; S, 4.58. Found: C, 56.37; H, 5.84; N, 7.69; S, 4.37. MS (ES^+) 723 (30%), 718 (100), 701 ($M^+ + 1$, 23), 645 (59).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-

- 599 -

MS (ES⁺) 712 (31%), 707 (100), 690 (M⁺ + 1, 41), 634 (55).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-

5 pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoic acid

(505b), was synthesized by a similar method as compound 217 to afford a colourless powder (499mg, 96%): mp. 95-145°C; [α]_D²² -137° (c 0.12, MeOH); IR (KBr) 3323,

10 2936, 1732, 1665, 1529, 1452, 1421, 1312, 1275, 1256, 1221, 1183, 1153, 1135, 1101, 990; ¹H NMR (CD₃OD) δ 7.67-7.56 (2H, m), 7.49-7.38 (4H, m), 5.23-5.12 (1H, m), 5.02 (1H, d), 4.79-4.73 (1H, m), 4.52-4.34 (3H, m), 3.48-3.25 (2H, m), 3.03-2.85 (2H, m), 2.94 (3H, s),
15 2.74 (3H, s), 2.79-2.66 (1H, m), 2.52-2.38 (1H, m), 2.29-2.14 (1H, m), 2.04-1.70 (4H, m). Anal. Calcd for C₂₇H₃₁N₅O₁₁S•H₂O: C, 49.77; H, 5.18; N, 10.75; S, 4.92. Found: C, 49.83; H, 5.01; N, 10.27; S, 4.84. MS (ES⁺) 746 (42%), 632 (M - 1, 100), 386 (60). Accurate mass
20 calculated for C₂₇H₃₂N₅O₁₁S (MH⁺): 634.1819. Found: 634.1807.

[3S,4RS(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-

25 hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (503c), was synthesized by a similar method as compound 213e to afford a colourless solid (446mg, 84%): IR (KBr) 3345, 2976, 2935, 1727, 1664, 1603, 1535, 1483, 1451, 1416, 1395, 1369, 1328, 1297, 1277, 1237, 1155, 1135, 1076,
30 990, 755; ¹H NMR (CDCl₃) δ 7.98-7.89 (1H, m), 7.55-7.45

- 598 -

- (methanesulphonylamino)-1-carboxamido]-4-hydroxy-5-(5-methyl-3-phenylisoxazoyloxy)pentanoate (503b), was synthesized by a similar method as compound 213e, to afford an off-white powder (671mg, 88%): mp. 90-120°C;
- 5 IR (KBr) 3345, 2977, 1727, 1664, 1532, 1450, 1423, 1369, 1323, 1310, 1276, 1257, 1154, 1101, 990, 766; ¹H NMR (CDCl₃) δ 7.61-7.55 (2H, m), 7.51-7.42 (3H, m), 6.86 (1H, d), 5.69 (1H, d), 5.21 (1H, m), 4.64-4.38 (2H, m), 4.15-4.05 (3H, m), 3.84 (1H, s), 3.31-3.14 (2H, m),
- 10 2.97-2.87 (1H, m), 2.94 (3H, s), 2.76 (3H, s), 2.64-2.48 (3H, m), 2.39-2.29 (1H, m), 2.04-1.61 (5H, m). Anal. Calcd for C₃₁H₄₁N₅O₁₁S•H₂O: C, 52.46; H, 6.11; N, 9.87; S, 4.52. Found: C, 52.34; H, 5.92; N, 9.56; S, 4.44. MS (ES⁺) 714 (47%), 692 (M⁺ + 1, 84), 636 (100).
- 15 [3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoate (504b), was synthesized by a similar method as compound 216b to
- 20 afford a colourless powder (601mg, 93%): mp. 75-115°C; [α]_D²³ -104° (c 0.26, CH₂Cl₂); IR (KBr) 3324, 2977, 2935, 1730, 1670, 1525, 1452, 1422, 1369, 1317, 1276, 1256, 1222, 1155, 1107, 990, 766; ¹H NMR (CDCl₃) δ 7.68-7.61 (2H, m), 7.47-7.38 (3H, m), 7.32-7.24 (1H, m),
- 25 5.56 (1H, d), 5.36-5.24 (1H, m), 5.04 (1H, d), 4.88 (1H, d), 4.86-4.77 (1H, m), 4.64-4.39 (2H, m), 3.32-3.17 (1H, m), 2.97-2.85 (1H, m), 2.93 (3H, s), 2.76 (3H, s), 2.80-2.71 (1H, m), 2.65-2.49 (1H, m), 2.41-2.30 (1H, m), 2.12-1.61 (6H, m), 1.42 (9H, s). Anal.
- 30 Calcd for C₃₁H₃₉N₅O₁₁S•H₂O: C, 52.61; H, 5.84; N, 9.90; S, 4.53. Found: C, 52.94; H, 5.69; N, 9.72; S, 4.51.

11 / 11

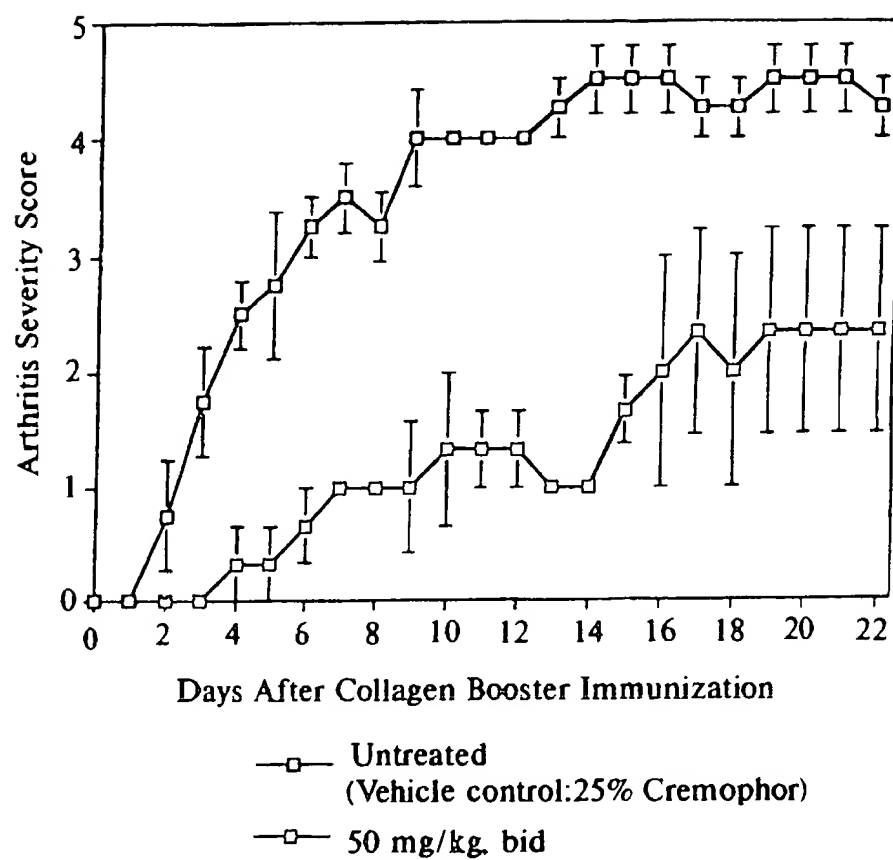


FIG. 14

10/11

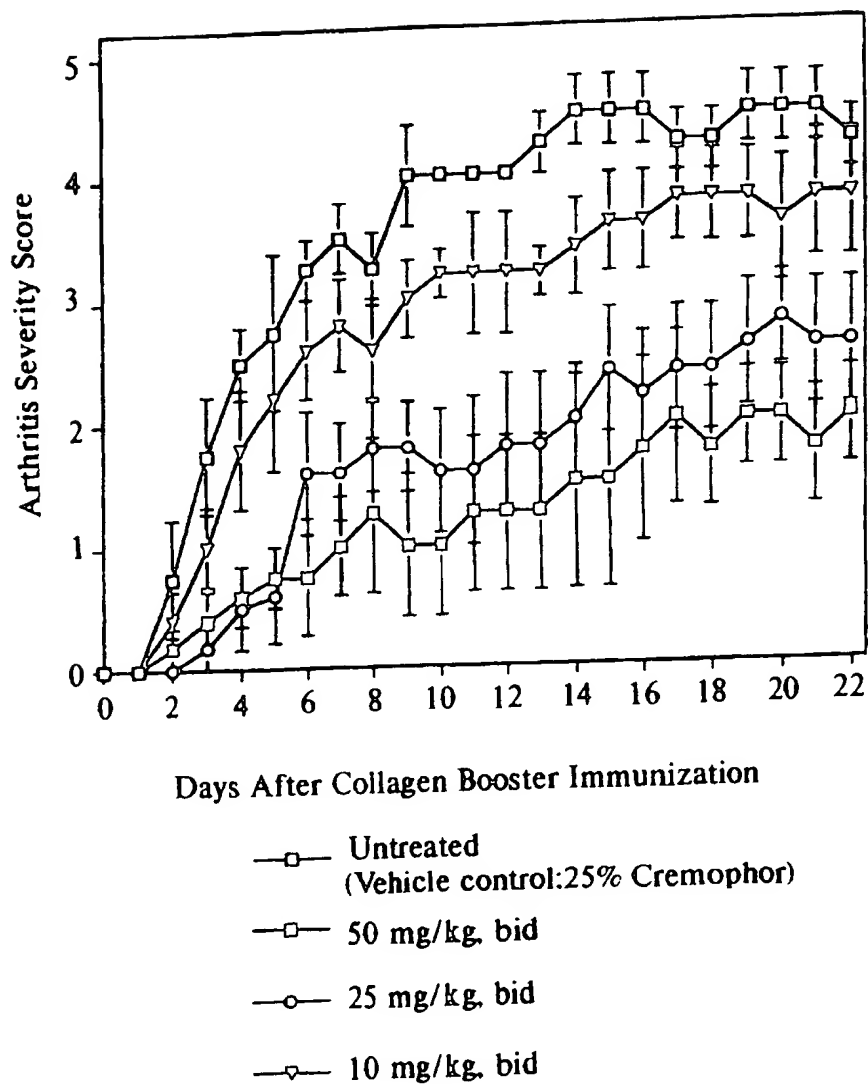


FIG. 13

9/11

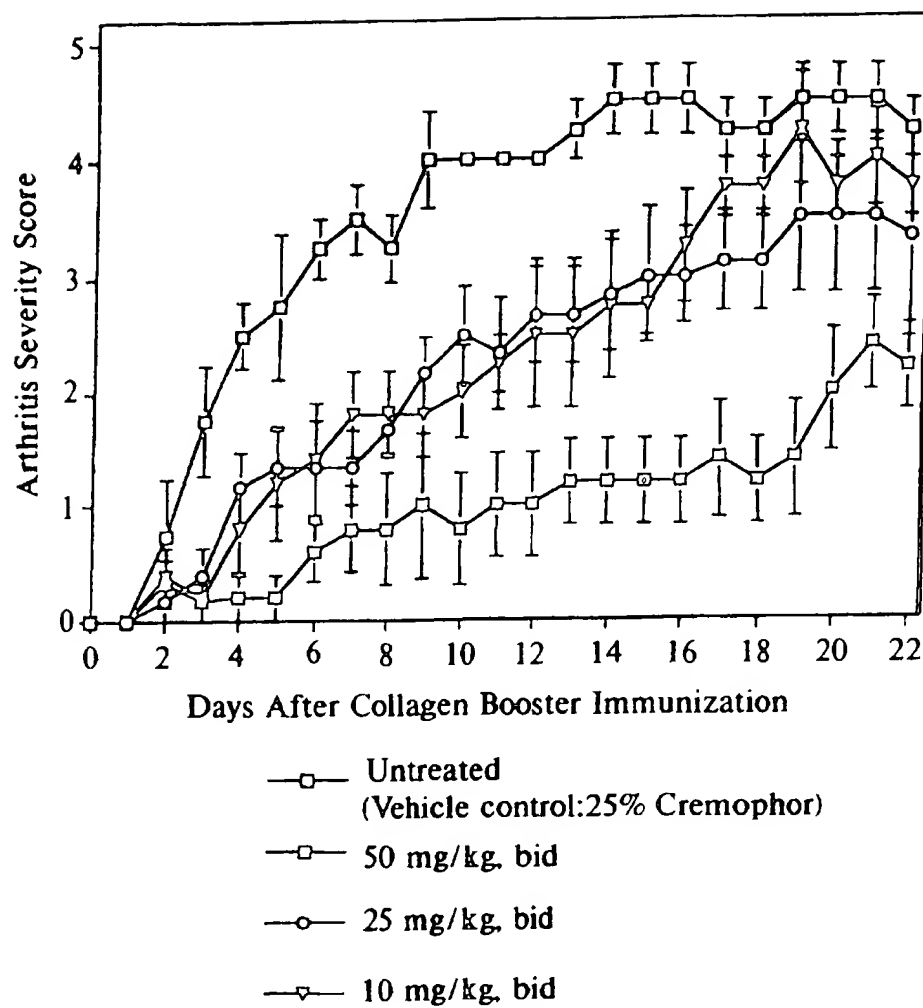


FIG. 12

8 / 11

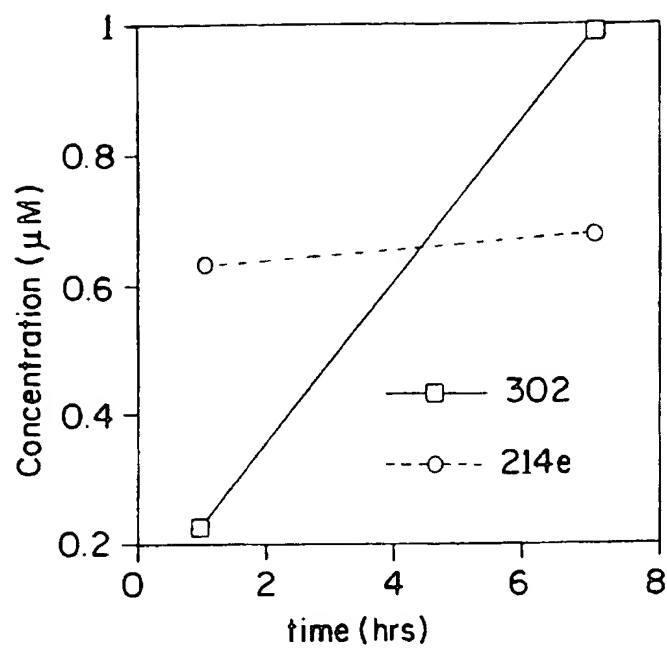


FIG. 11A

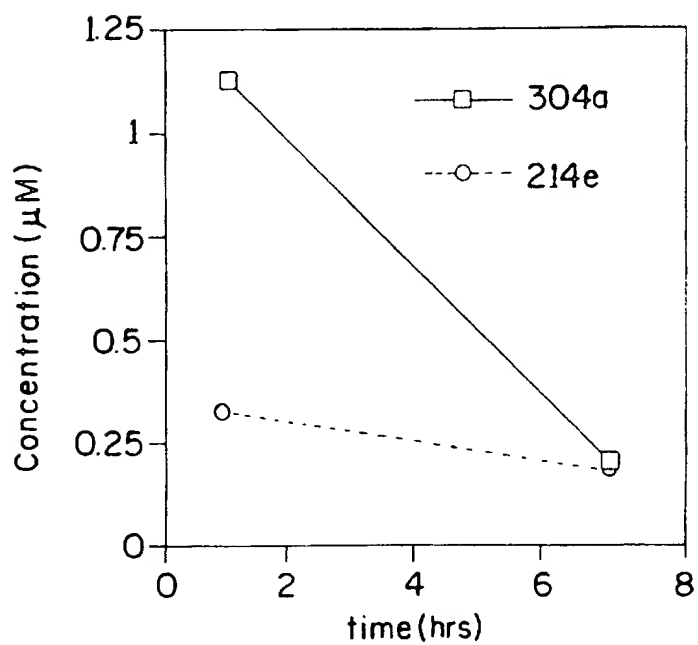


FIG. 11B

7/11

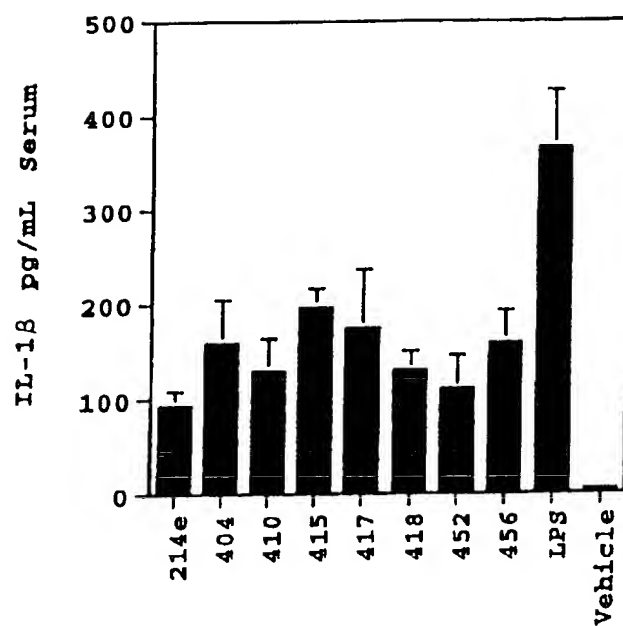


FIG. 10

6 / 11

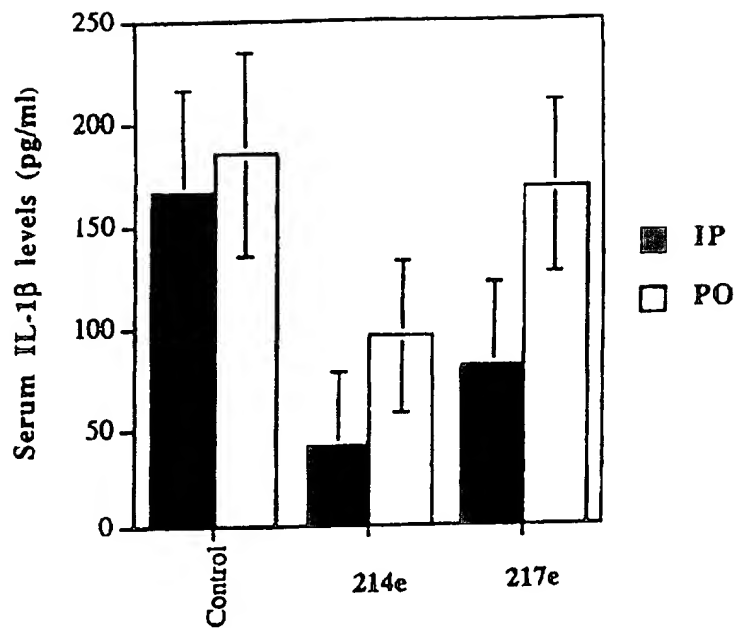


FIG. 8

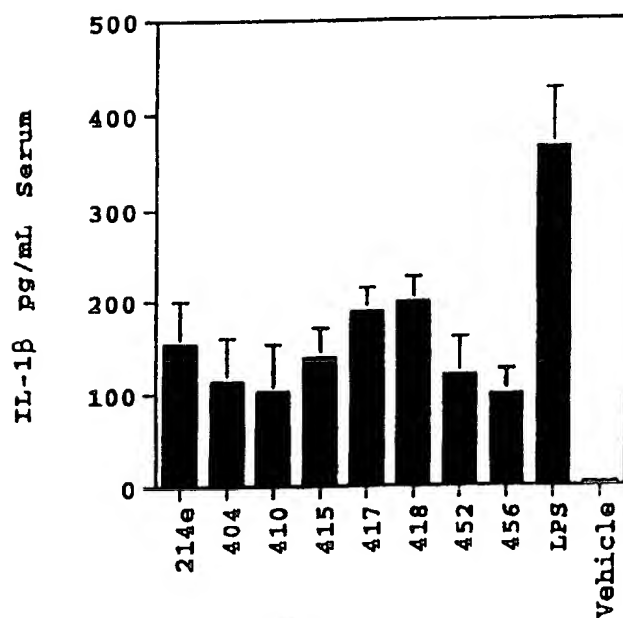


FIG. 9

5 / 11

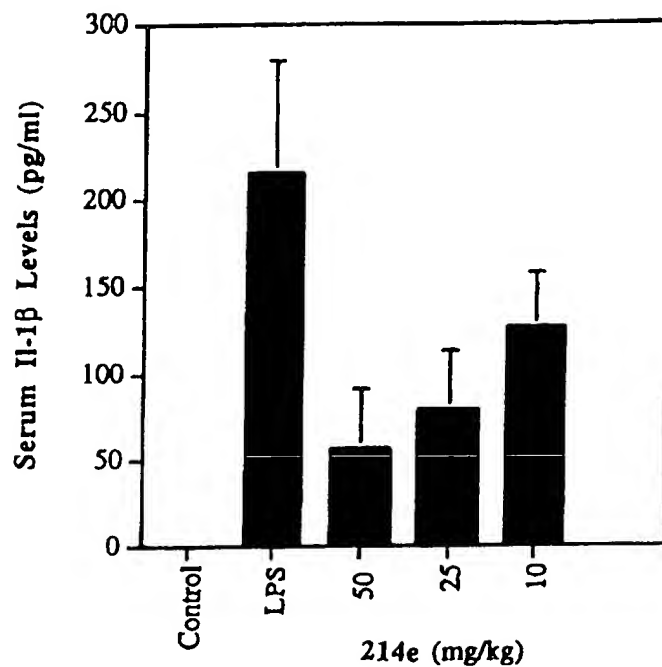


FIG. 6

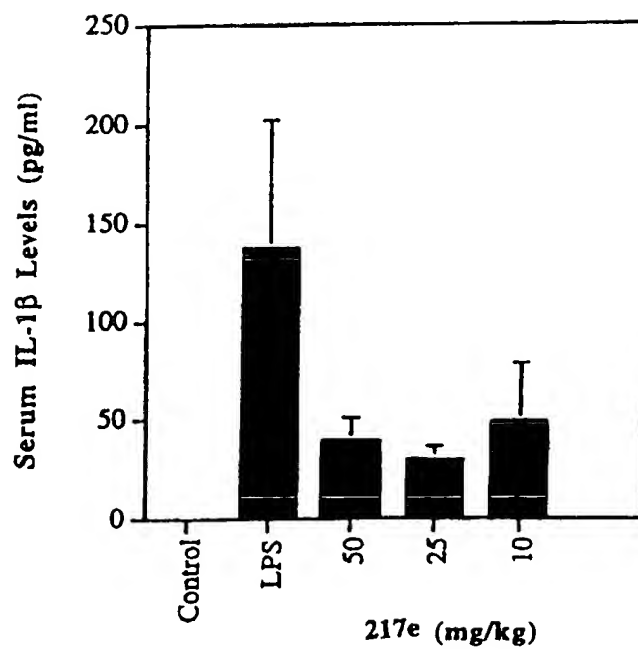


FIG. 7

4 / 11

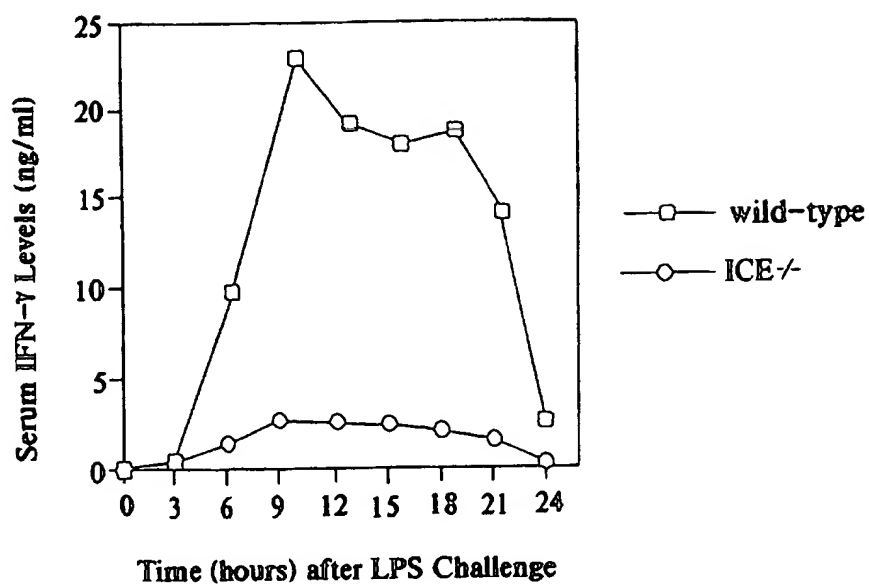


FIG. 4

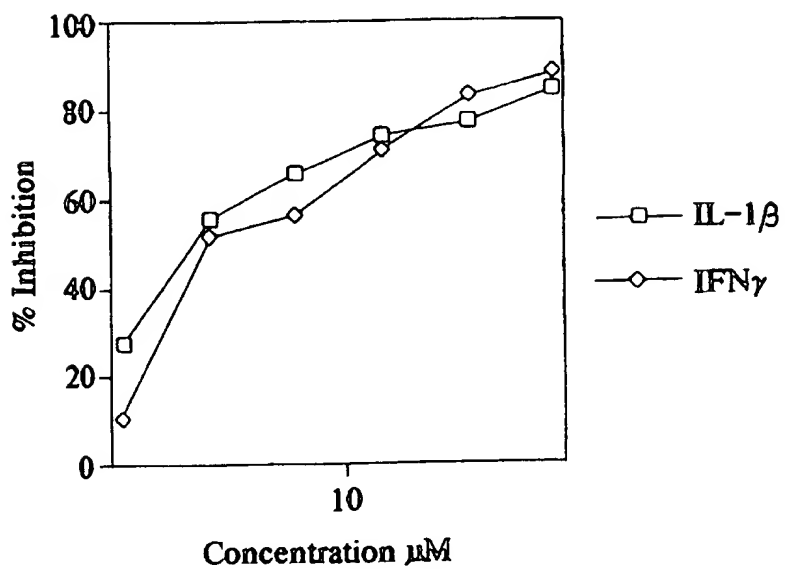


FIG. 5

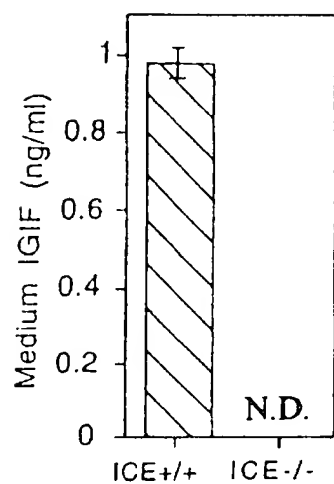


FIG. 3A

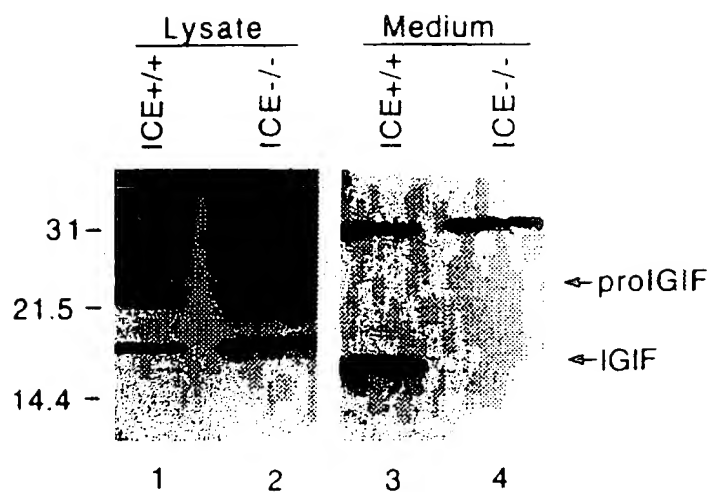


FIG. 3B

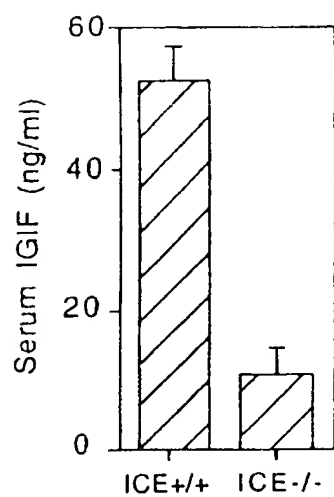


FIG. 3C

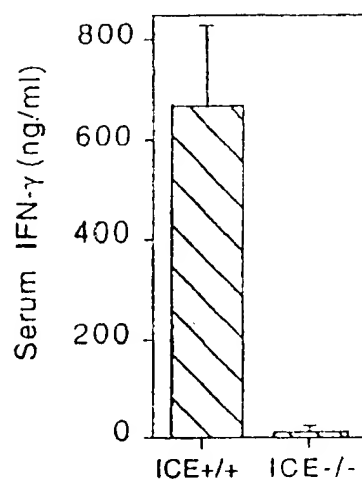


FIG. 3D

2/11

FIG. 2A

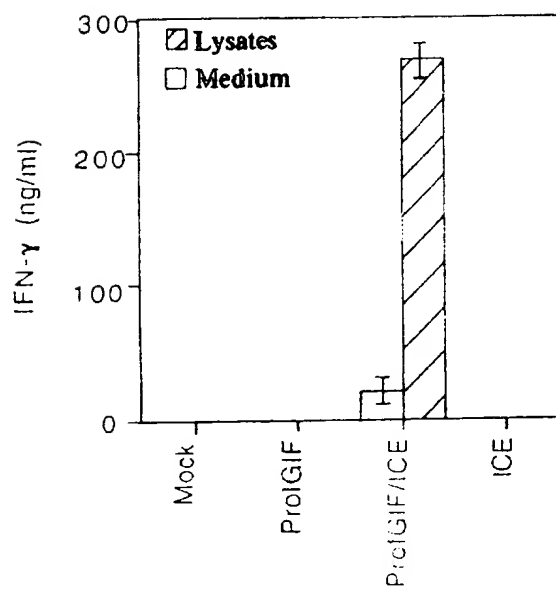
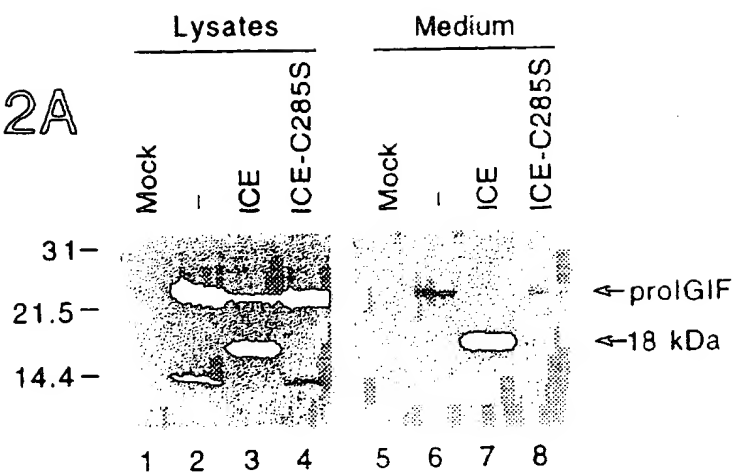


FIG. 2B

1 / 11

FIG. 1A

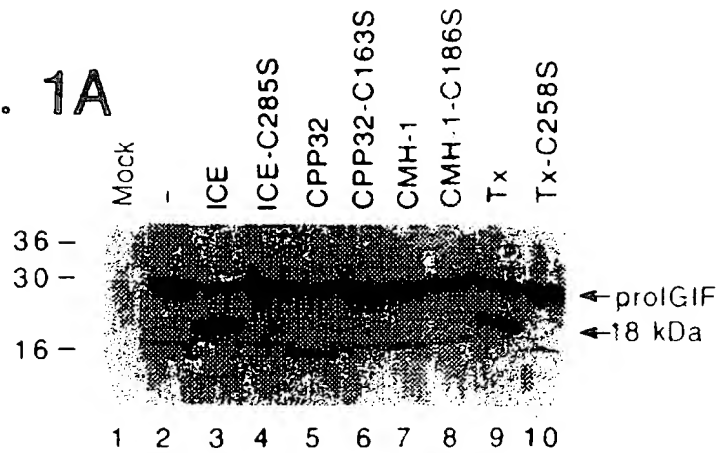


FIG. 1B

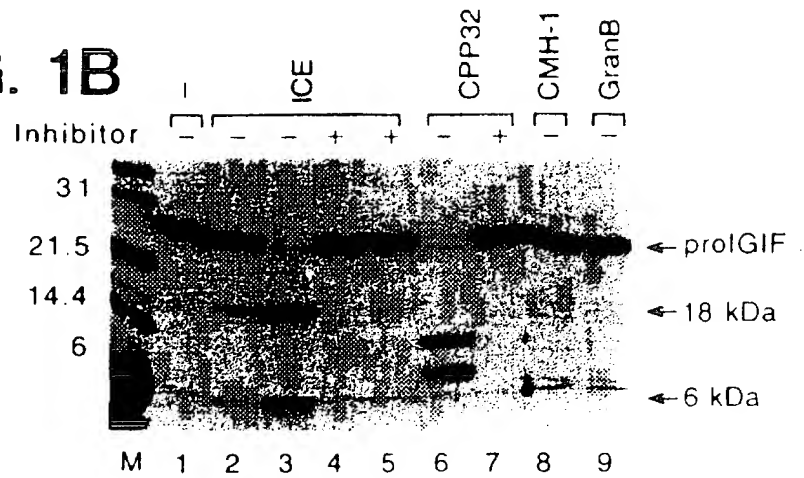
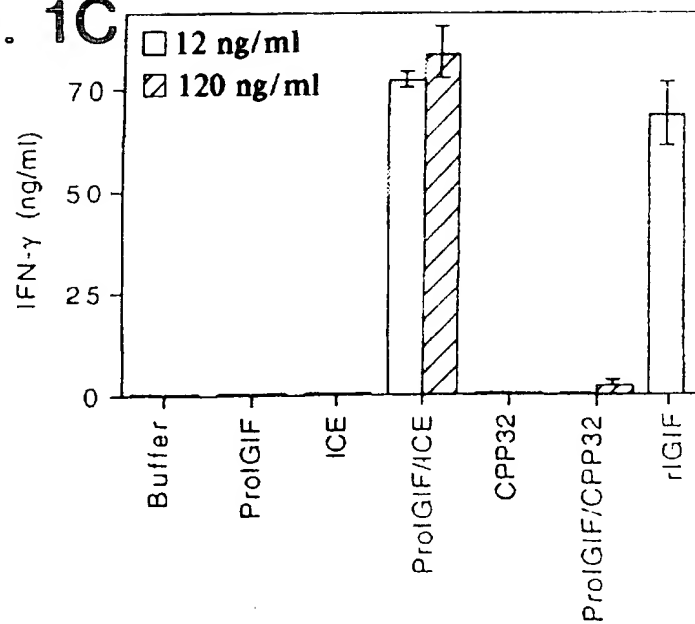
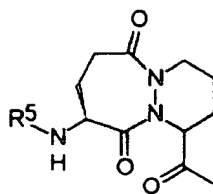


FIG. 1C



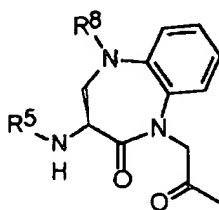
- 934 -

(A-e10)



153. The process according to any one of claims 140-149, wherein R₁ is:

5 (A-w2)

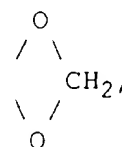


- 933 -

comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

5 each Q_1 is independently selected from the group consisting of $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{I}$, $-\text{NO}_2$, $-\text{CN}$, $=\text{O}$, $-\text{OH}$, -perfluoro C_{1-3} alkyl, R_5 , $-\text{OR}_5$, $-\text{NHR}_5$, $-\text{OR}_9$, $-\text{N}(\text{R}_9)(\text{R}_{10})$, $-\text{R}_9$, $-\text{C}(\text{O})-\text{R}_{10}$, and

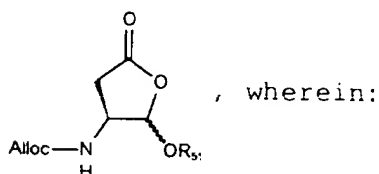
10



15 provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$;

151. The process according to any one of claims 140 -149 wherein the N-alloc protected amine is:

20



R_{51} is independently selected from the group consisting of R_9 , $-\text{C}(\text{O})-\text{R}_9$, $-\text{C}(\text{O})-\text{N}(\text{H})-\text{R}_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing $-\text{O}-$, $-\text{S}-$, or $-\text{NH}-$;

25

152. The process according to any one of claims 140-149, wherein R_1 is:

- 932 -

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

5 each R_{10} is independently selected from the group consisting of $-H$, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

10 R_{13} is selected from the group consisting of H , Ar_3 , and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OF_5$, $-OH$, $-OR_9$, or $-CO_2H$;

15 each R_{51} is independently selected from the group consisting of R_9 , $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing $-O-$, $-S-$, or $-NH-$;

20 each R_{21} is independently selected from the group consisting of $-H$ or a $-C_{1-6}$ straight or branched alkyl group;

25 each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally

- 931 -

5 -C(O)O-R₉,
 -C(O)-N(R₁₀)(R₁₀)
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-O-R₉,
 -C(O)C(O)-R₁₀,
 -R₉,
 -H,
 -C(O)C(O)-OR₁₀, and
 10 -C(O)C(O)-N(R₉)(R₁₀);

X₅ is CH or N;

Y₂ is H₂ or O;

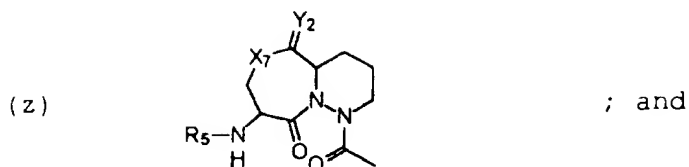
15 X₇ is -N(R₈)- or -O-;

R₆ is selected from the group consisting of -H and
 -CH₃;

R₈ is selected from the group consisting of:

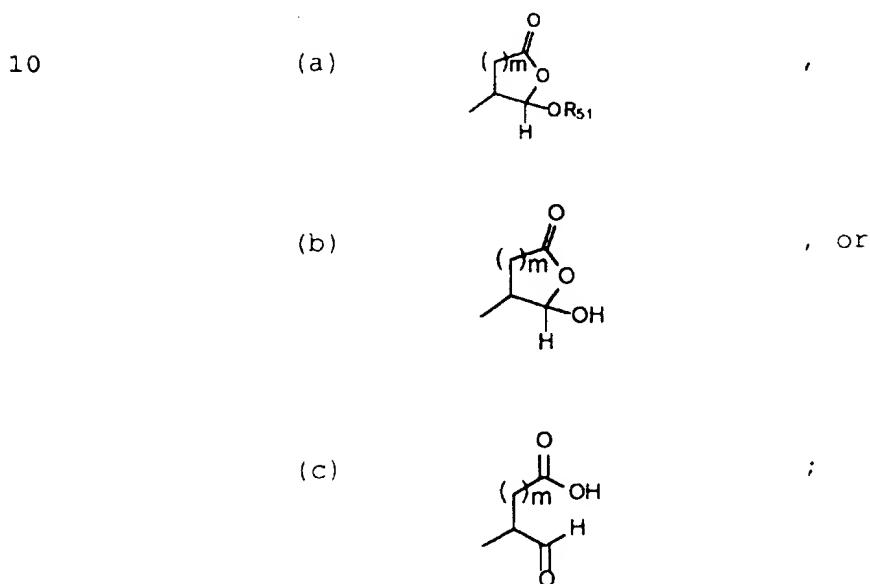
20 -C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-N(H)-R₁₀,
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 25 -C(O)C(O)-R₁₀;
 -C(O)-CH₂N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 -C(O)-CH₂C(O)-R₉,
 -H, and
 30 -C(O)-C(O)-OR₁₀;

- 930 -



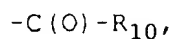
C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being
 5 singly or multiply substituted by halogen, -NH₂, or -NH-R₉;

R₂ is:



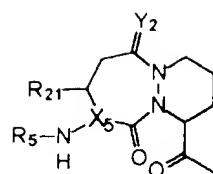
15 m is 1 or 2;

each R₅ is independently selected from the group consisting of:



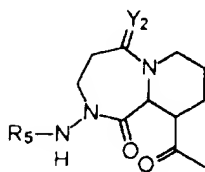
- 929 -

(e10)



;

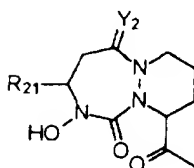
(e11)



;

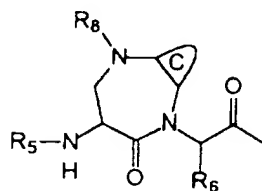
5

(e12)



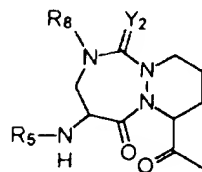
;

(w2)



;

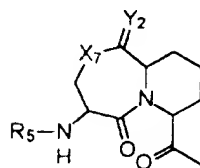
(y1)



;

10

(y2)



;

- 928 -

of CH₂Cl₂ and DMF.

145. The process according to claim 144, wherein the nucleophilic scavenger is dimethyl barbituric acid.

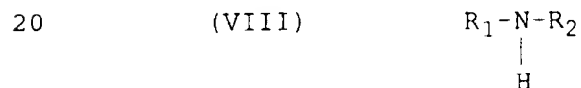
5 146. The process according to claim 145, wherein the solution comprises trifluoroacetic acid in about 1-90% by weight.

10 147. The process according to claim 146, wherein the solution comprises trifluoroacetic acid in about 20-50% by weight.

148. The process according to claim 145, wherein the solution comprises hydrochloric acid in about 0.1-30% by weight.

15 149. The process according to claim 148, wherein the solution comprises hydrochloric acid in about 5-15% by weight.

150. The process according to any one of claims 140-149, wherein the N-acylamino compound is represented by formula (VIII):



wherein:

25 R₁ is selected from the group consisting of the following formulae:

- 927 -

diabetes mellitus (Type I), juvenile diabetes, psoriasis, graft vs. host disease, and hepatitis.

140. A process for preparing an N-acylamino compound, comprising the steps of:

- 5 a) mixing a carboxylic acid with an N-alloc-protected amine in the presence of an inert solvent, triphenylphosphine, a nucleophilic scavenger, and tetrakis-triphenyl phosphine palladium(0) at ambient temperature under an inert atmosphere; and
- 10 b) adding to the step a) mixture, HOBT and EDC; and optionally comprising the further step of:
- 15 c) hydrolyzing the step b) mixture in the presence of a solution comprising an acid and H₂O, wherein the step b) mixture is optionally concentrated.

141. The process according to claim 140, wherein the inert solvent is CH₂Cl₂, DMF, or a mixture of CH₂Cl₂ and DMF.

20 142. The process according to claim 140, wherein the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine or dimethyl barbituric acid.

25 143. The process according to claim 142, wherein the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

144. The process according to claim 142, wherein the inert solvent is CH₂Cl₂, DMF, or a mixture

- 926 -

production and a pharmaceutically acceptable carrier.

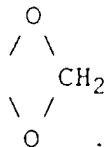
138. A method for treating or preventing a disease selected from an IGIF mediated disease, an IFN- γ mediated disease, an inflammatory disease, an autoimmune disease, an infectious disease, a proliferative disease, a neurodegenerative disease, a necrotic disease, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative collitis, cerebral ischemia, myocardial ischemia, adult respiratory distress syndrome, infectious hepatitis, sepsis, septic shock, Shigellosis, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome comprising the step of administering to said patient a pharmaceutical composition according to claims 136 or 137.

139. The method according to claim 138, wherein the disease is selected from an inflammatory disease, an autoimmune disease, an infectious disease, rheumatoid arthritis, ulcerative collitis, Crohn's disease, hepatitis, adult respiratory distress syndrome, glomerulonephritis, insulin-dependent

- 925 -

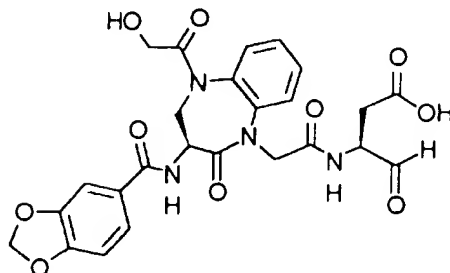
cyclic group is phenyl, substituted by

5



134. The compound according to claim 133, wherein the compound is:

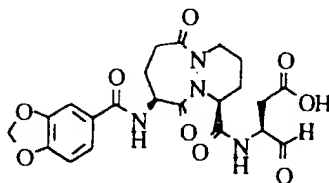
910



10

135. The compound according to claim 133, wherein the compound is:

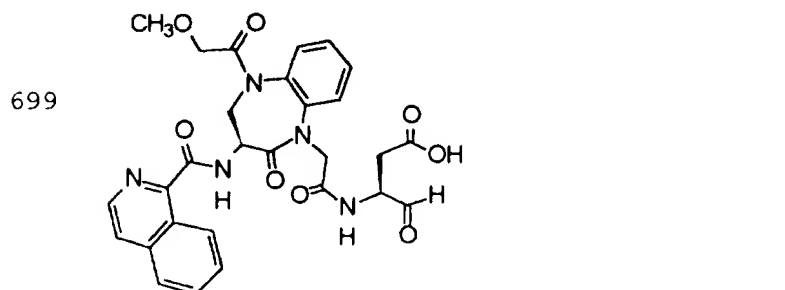
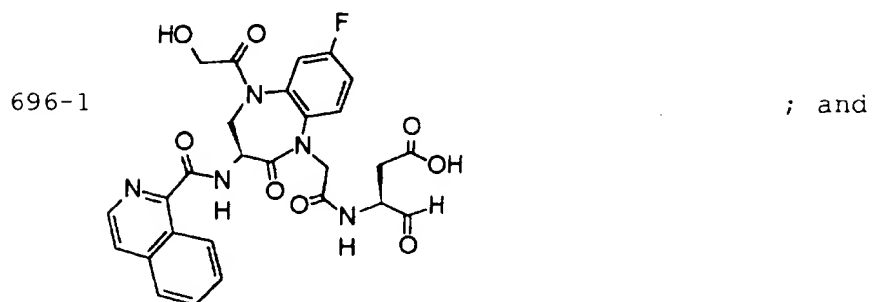
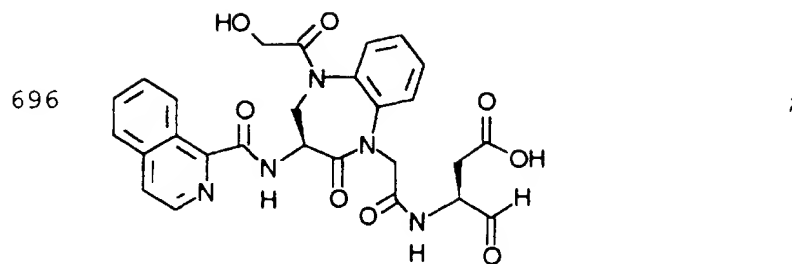
415



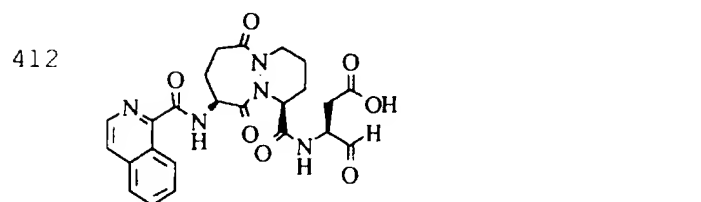
136. A pharmaceutical composition, comprising a compound according to any one of claims 1-41 and 57-135 in an amount effective for decreasing IGIF production and a pharmaceutically acceptable carrier.

137. A pharmaceutical composition comprising a compound according to any one of claims 1-41 and 57-135 in an amount effective for decreasing IFN- γ

- 924 -



132. The compound according to claim 130,
5 wherein the compound is:

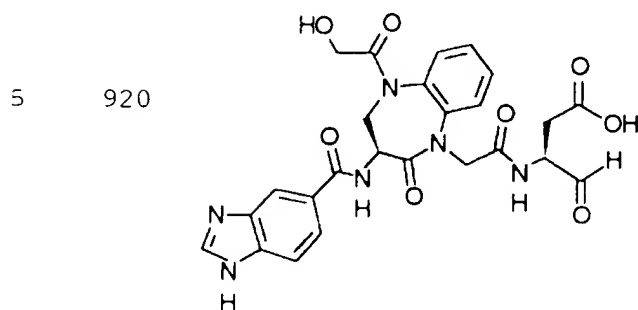
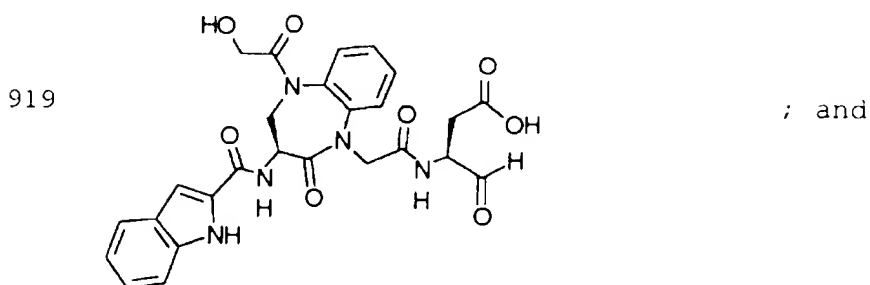


133. The compound according to claim 119,
wherein R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3

- 923 -

by $-Q_1$.

129. The compound according to claim 128, selected from the group consisting of:

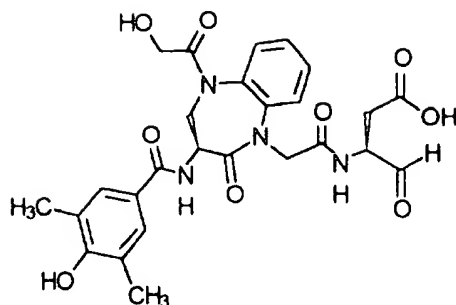


130. The compound according to claim 128, wherein the Ar_3 cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

10 131. The compound according to claim 130, wherein the compound is:

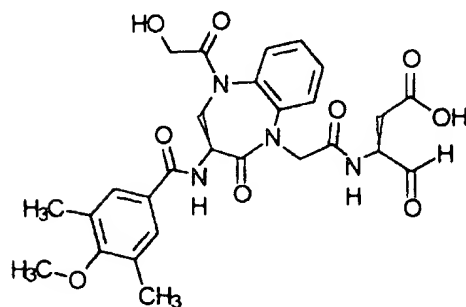
- 922 -

917



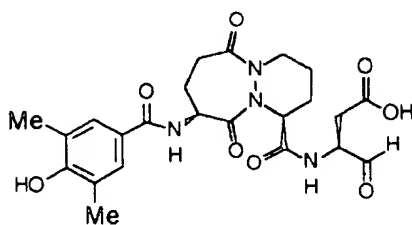
; and

922



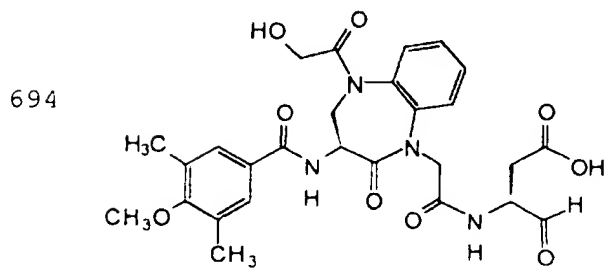
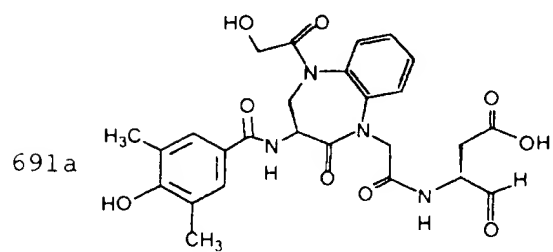
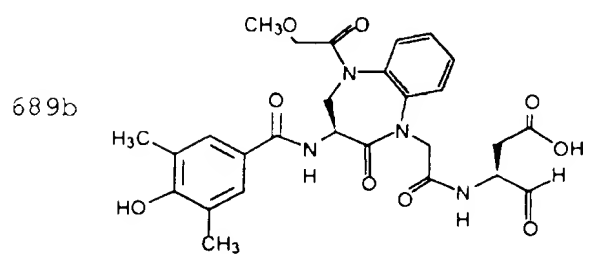
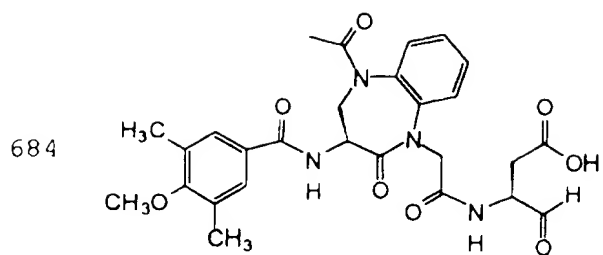
127. The compound according to claim 125,
wherein the compound is:

5 214w



128. The compound according to claim 119,
wherein:

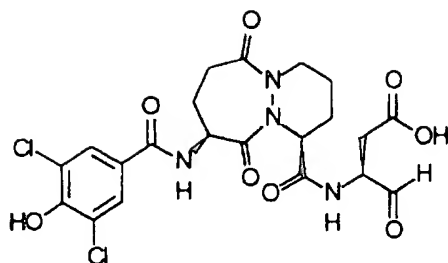
10 R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3
cyclic group is selected from the group consisting of
is indolyl, benzimidazolyl, thienyl, quinolyl,
isoquinolyl and benzo[b]thiophenyl, and said cyclic
group optionally being singly or multiply substituted



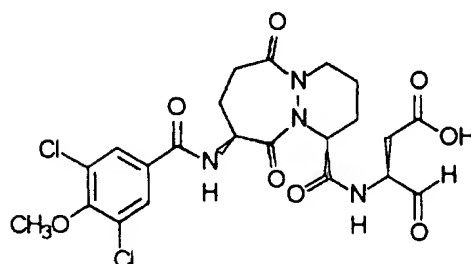
- 920 -

214k

; and



214m

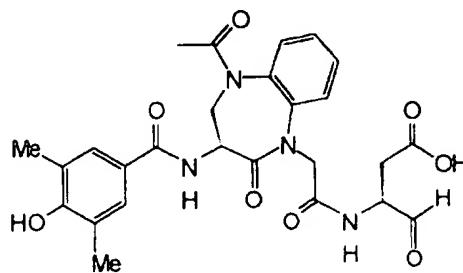


125. The compound according to claim 120,
 wherein Ar₃ is phenyl being singly or multiply
 5 substituted at the 3- or 5-position by -R₉, wherein R₉
 is a C₁₋₄ straight or branched alkyl group;
 and at the 4-position by -O-R₅.

126. The compound according to claim 125,
 selected from the group consisting of:

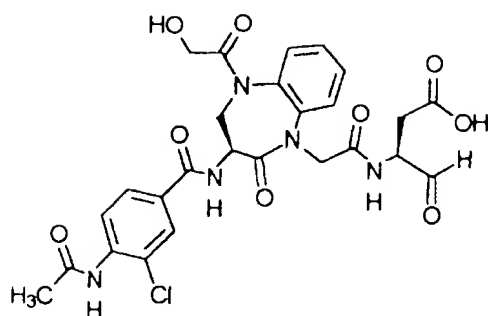
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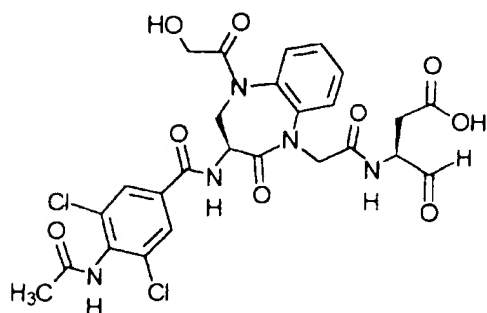


- 919 -

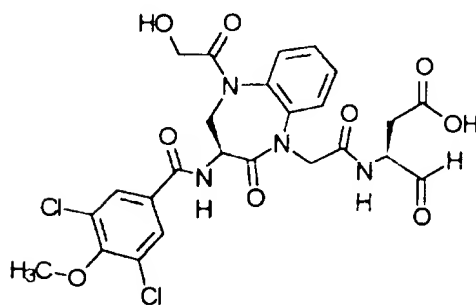
914



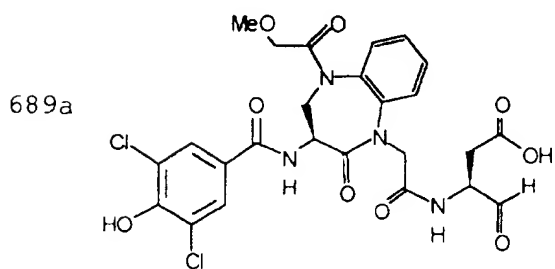
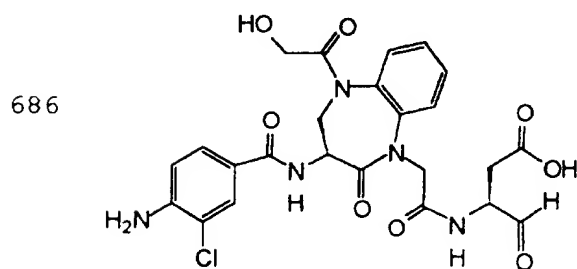
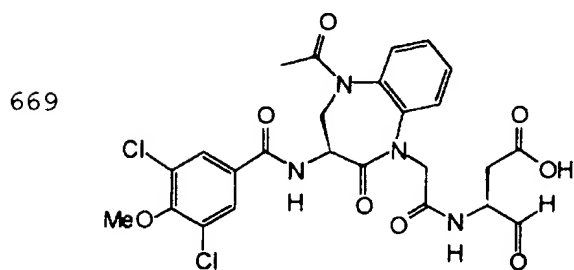
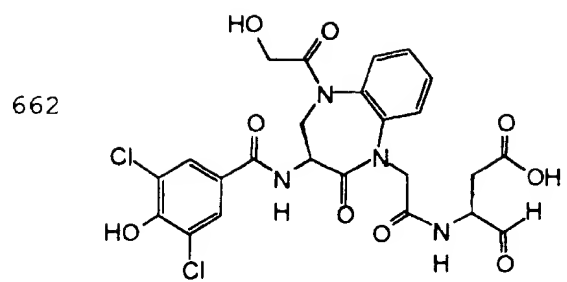
915



918

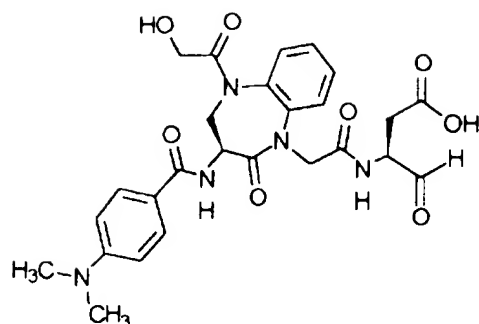


124. The compound according to claim 122,
 5 selected from the group consisting of:



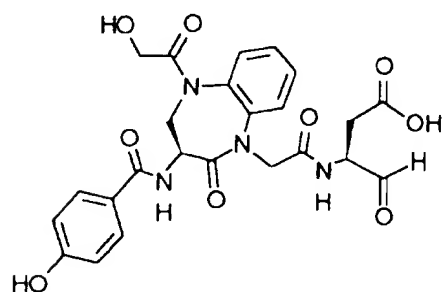
- 917 -

913



; and

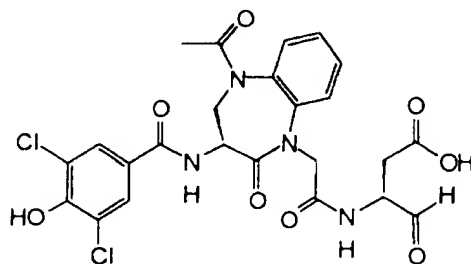
916



122. The compound according to claim 120,
 wherein Ar₃ is phenyl being singly or multiply
 5 substituted at the 3- or 5-position by -Cl or at the 4-
 position by -NH-R₅, -N(R₉)(R₁₀), or -O-R₅.

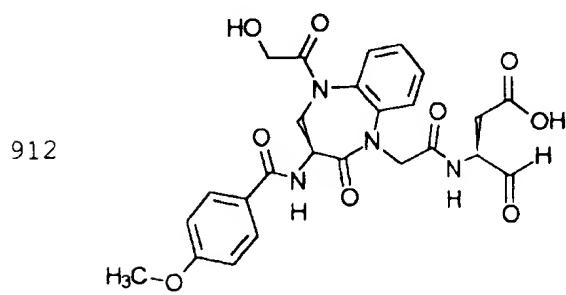
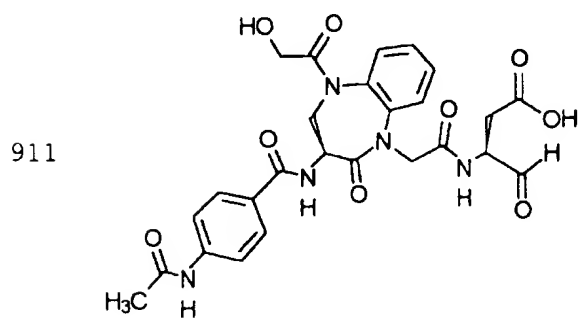
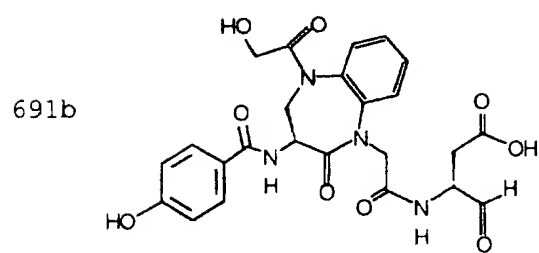
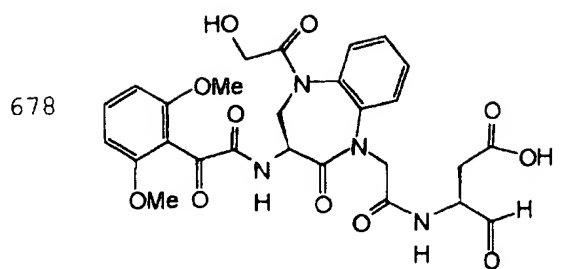
123. The compound according to claim 122,
 selected from the group consisting of:

656



;

- 916 -



- 915 -

119. The compound according to claim 118,
wherein R_{10} is Ar_3 .

120. The compound according to claim 119,
wherein:

5 R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3 , wherein the Ar_3
cyclic group is phenyl optionally being singly or
multiply substituted by:

$-R_9$, wherein R_9 is a C_{1-4} straight or branched
alkyl group;

10 $-F$,

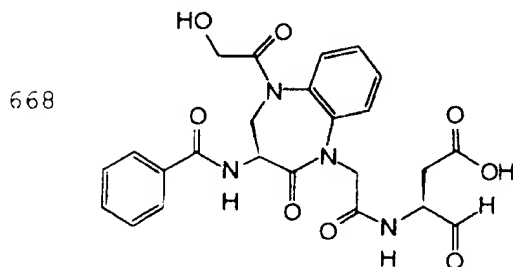
$-Cl$,

$-N(H)-R_5$, wherein $-R_5$ is $-H$ or $-C(O)-R_{10}$, wherein
 R_{10} is a $-C_{1-6}$ straight or branched alkyl group
optionally substituted with $-Ar_3$, wherein Ar_3 is
15 phenyl,

$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a
 $-C_{1-4}$ straight or branched alkyl group, or

$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or
branched alkyl group.

20 121. The compound according to claim 120,
selected from the group consisting of:



- 914 -

and said cyclic group being singly or multiply substituted by

$-Q_1$;

each Q_1 is independently selected from the group
 5 consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$
 wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is
 $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and



wherein each R_9 and R_{10} are independently a $-C_{1-6}$
 straight or branched alkyl group optionally substituted
 15 with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1
 group which comprises one or more additional $-Ar_3$
 groups, said additional $-Ar_3$ groups are not substituted
 20 with another $-Ar_3$.

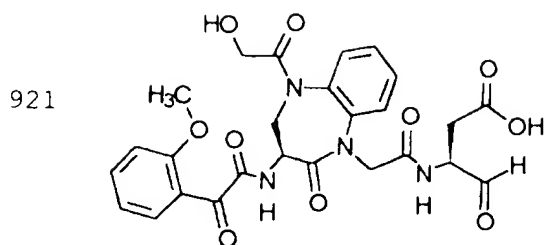
115. The compound according to claim 114,
 wherein R_3 is $-C(O)-Ar_2$,

116. The compound according to claim 114,
 wherein R_3 is $-C(O)CH_2-T_1-R_{11}$;

25 117. The compound according to claim 114,
 wherein R_3 is $-C(O)-H$.

118. The compound according to any one of
 claims 104-117, wherein R_5 is $-C(O)-R_{10}$ or
 $-C(O)C(O)-R_{10}$.

- 913 -



113. The compound according to claim 111,
wherein R_8 is $-C(O)-CH_2-OR_{10}$ and R_{10} is $-H$ or $-CH_3$.

114. The compound according to claim 68,
5 wherein:

m is 1;

T_1 is O or S;

R_{21} is $-H$ or $-CH_3$;

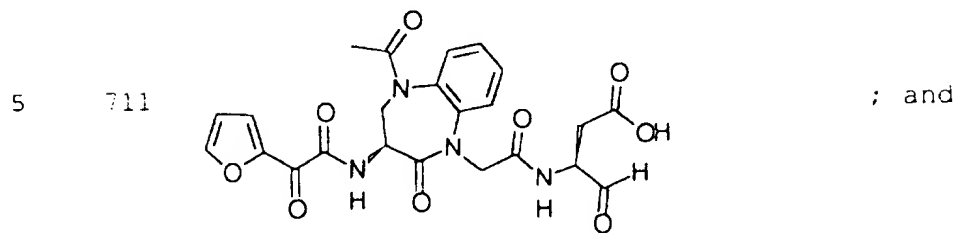
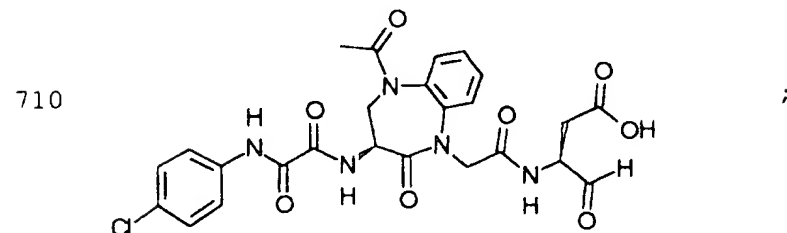
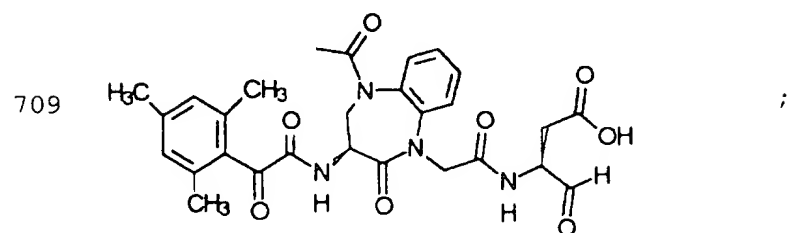
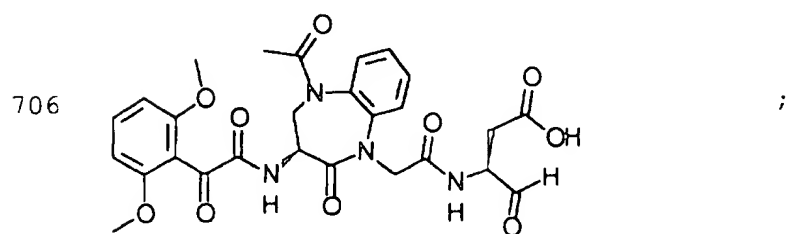
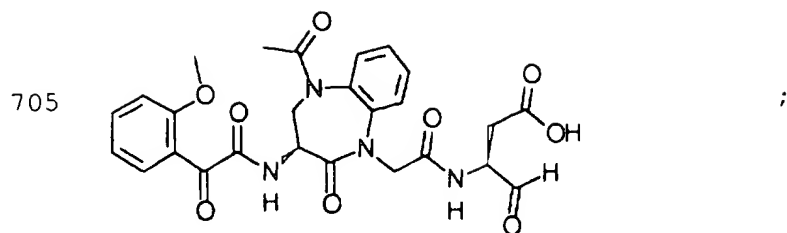
10 Ar_2 is (hh);

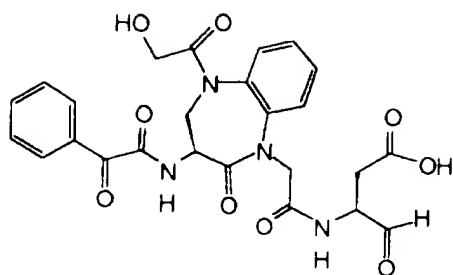
Y is O;

each Ar_3 cyclic group is independently selected
from the set consisting of phenyl, naphthyl, thienyl,
15 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,
isoxazolyl, benzotriazolyl, benzimidazolyl,
thienothienyl, imidazolyl, thiadiazolyl,
benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl
and said cyclic group being singly or multiply
20 substituted by $-Q_1$;

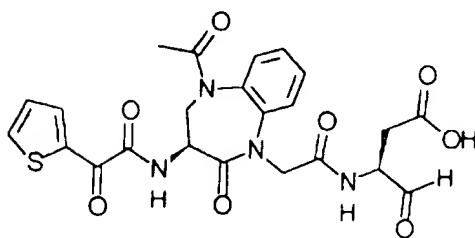
each Ar_4 cyclic group is independently selected
from the set consisting of phenyl, tetrazolyl,
pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl

- 912 -

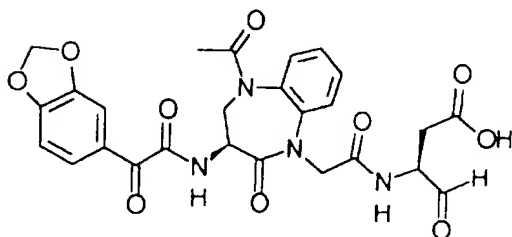




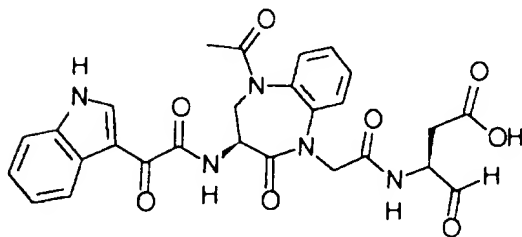
1



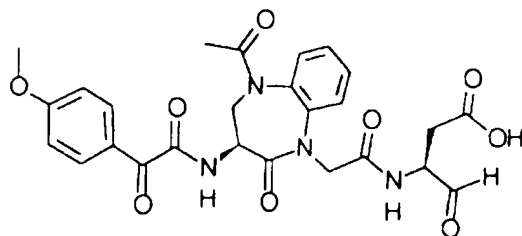
2



2



704



- 910 -

-C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-CH₂-OR₁₀, and
 -C(O)-CH₂C(O)-R₉.

5 107. The compound according to claim 106,
 wherein R₈ is -C(O)-CH₂-OR₁₀ and R₁₀ is -H or -CH₃.

108. The compound according to claim 105,
 wherein R₃ is -C(O)-Ar₂,

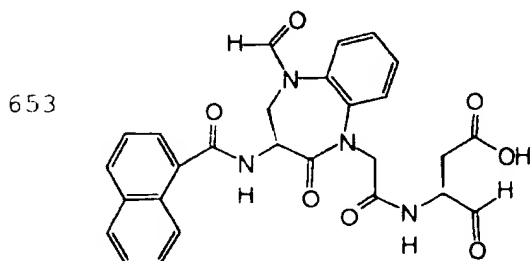
109. The compound according to claim 105,
 10 wherein R₃ is -C(O)CH₂-T₁-R₁₁;

110. The compound according to claim 105,
 wherein R₃ is -C(O)-H.

111. The compound according to claim 110,
 wherein R₈ is selected from the group consisting of:

15 -C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-CH₂-OR₁₀, and
 -C(O)-CH₂C(O)-R₉.

112. The compound according to claim 111,
 20 selected from the group consisting of:



- 909 -

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and



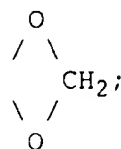
wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

106. The compound according to claim 105, wherein R₈ is selected from the group consisting of:

- 908 -

=O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, -OR₉,
 -N(R₉)(R₁₀), -R₉, -C(O)-R₁₀, and



5

provided that when -Ar₃ is substituted with a Q₁
 group which comprises one or more additional -Ar₃
 groups, said additional -Ar₃ groups are not substituted
 10 with another -Ar₃.

105. The compound according to claim 104,
 wherein:

m is 1;

C is a ring chosen from the set consisting of
 15 benzo, pyrido, and thieno, the ring optionally being
 singly or multiply substituted by halogen, -NH₂,
 -NH-R₅, or -NH-R₉, -OR₁₀, or -R₉, wherein R₉ is a
 straight or branched C₁₋₄ alkyl group, and R₁₀ is H or a
 straight or branched C₁₋₄ alkyl group;

20

T₁ is O or S;

R₆ is H;

R₁₁ is selected from the group consisting of -Ar₄,
 -(CH₂)₁₋₃-Ar₄, and -C(O)-Ar₄;

25

Ar₂ is (hh);

Y is O;

- 907 -

(ii)



wherein each Y is independently selected from the group consisting of O and S;

5 each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said
 10 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,
 15 and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3
 20 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally
 25 containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group
 30 consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN,

- 906 -

alkyl group optionally substituted with $-\text{Ar}_3$, wherein the $-\text{C}_{1-6}$ alkyl group is optionally unsaturated;

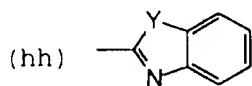
each R_{10} is independently selected from the group consisting of $-\text{H}$, $-\text{Ar}_3$, a $-\text{C}_{3-6}$ cycloalkyl group, and a
 5 $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, wherein the $-\text{C}_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

10 $-\text{Ar}_4$,
 $-(\text{CH}_2)_{1-3}-\text{Ar}_4$,
 $-\text{H}$, and
 $-\text{C}(\text{O})-\text{Ar}_4$;

R_{15} is selected from the group consisting of $-\text{OH}$,
 15 $-\text{OAr}_3$, $-\text{N}(\text{H})-\text{OH}$, and $-\text{OC}_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, $-\text{CONH}_2$, $-\text{OR}_5$, $-\text{OH}$, $-\text{OR}_9$, or $-\text{CO}_2\text{H}$;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or
 20 multiply substituted by $-\text{Q}_1$ or phenyl, optionally substituted by Q_1 :



, and

- 905 -

-C(O)O-R₉,
 -C(O)-N(R₁₀)(R₁₀)
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 5 -C(O)-CH₂-O-R₉,
 -C(O)C(O)-R₁₀,
 -R₉,
 -H,
 -C(O)C(O)-OR₁₀, and
 10 -C(O)C(O)-N(R₉)(R₁₀);

each T₁ is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

15 R₆ is selected from the group consisting of -H and -CH₃;

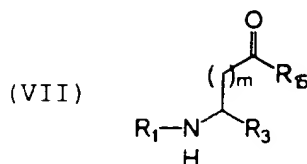
R₈ is selected from the group consisting of:

-C(O)-R₁₀,
 -C(O)O-R₉,
 20 -C(O)-NH-R₁₀,
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀,
 25 -C(O)-CH₂-N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 -C(O)-CH₂C(O)-R₉,
 -H, and
 -C(O)-C(O)-OR₁₀;

30 each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched

- 904 -

104. A compound represented by the formula:

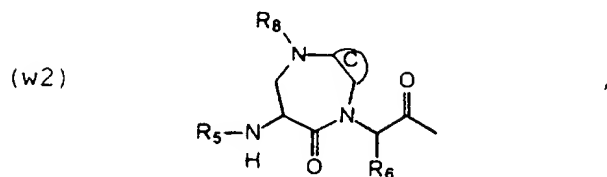


wherein:

m is 1 or 2;

5

R_1 is selected from the group consisting of the following formulae:



10

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being
15 singly or multiply substituted by -Q₁;

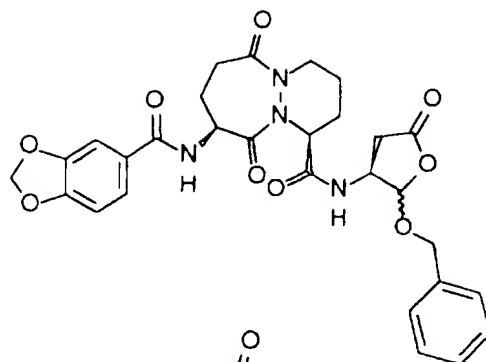
R_3 is selected from the group consisting of:

20

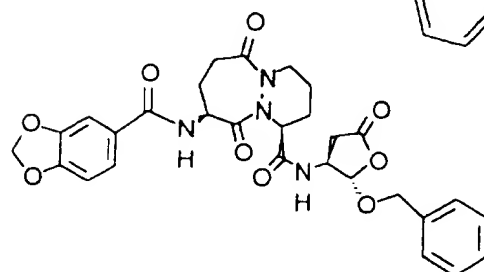
- CN,
- C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

each R_5 is independently selected from the group consisting of:

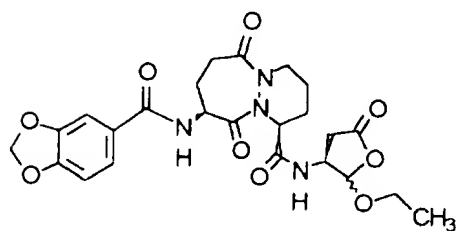
25 $-C(O)-R_{10},$



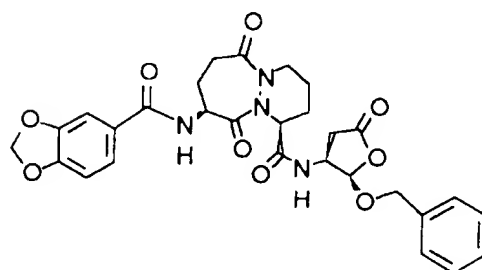
;



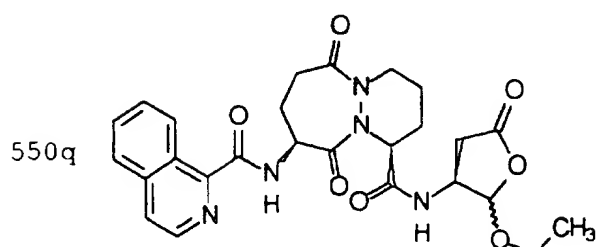
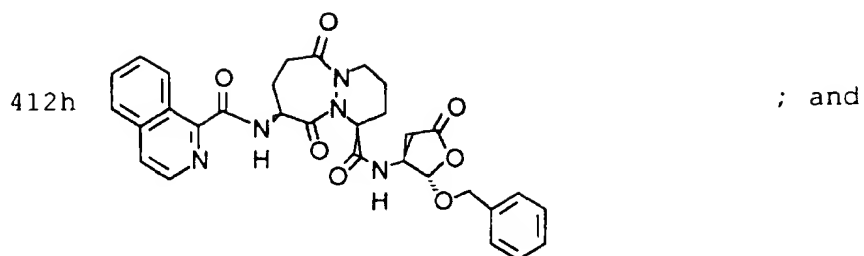
; and



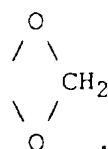
415C



- 902 -



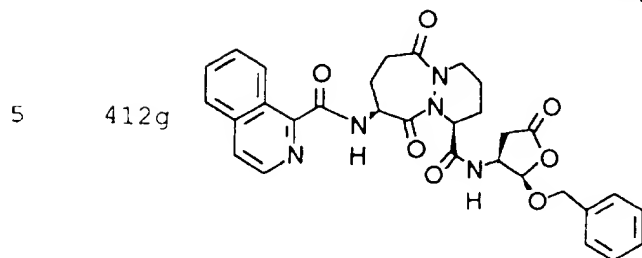
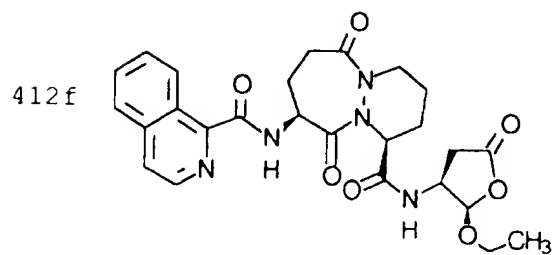
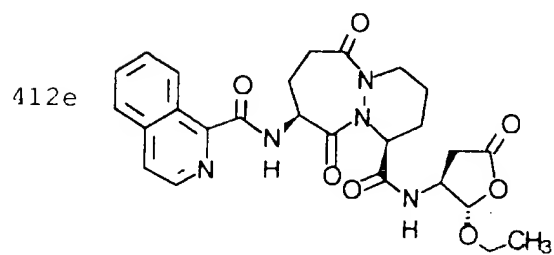
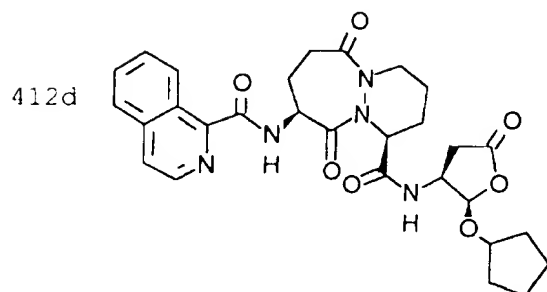
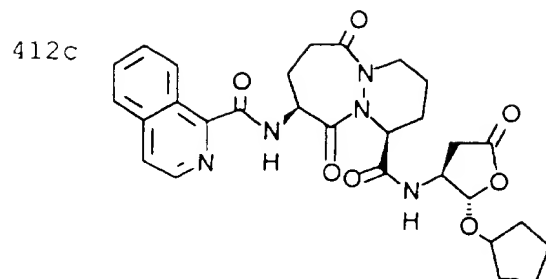
102. The compound according to claim 89,
 wherein R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3
 5 cyclic group is phenyl, substituted by

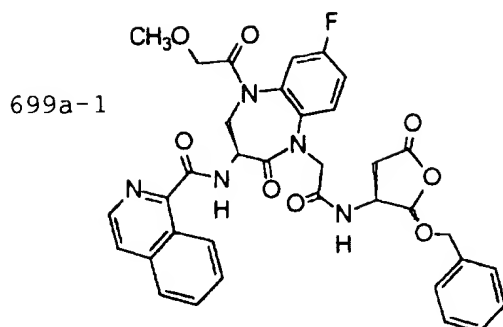


10

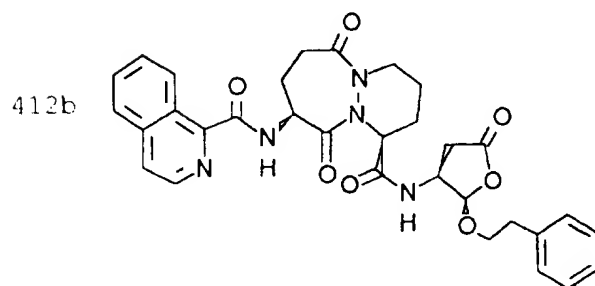
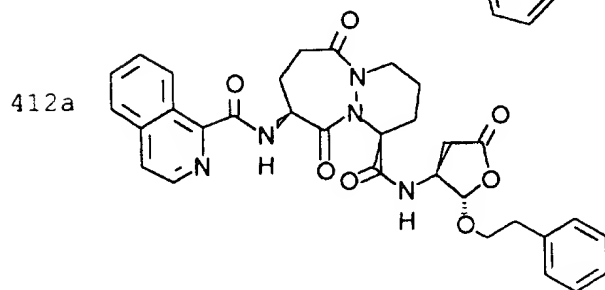
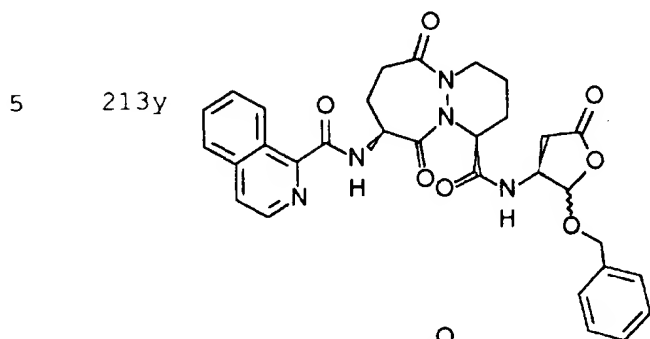
103. The compound according to claim 102,
 selected from the group consisting of:

- 901 -

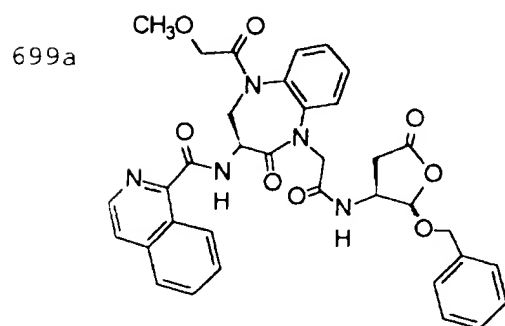
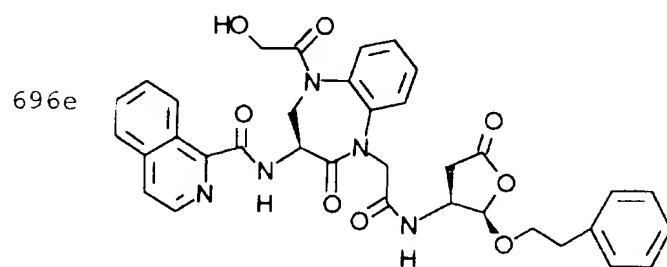
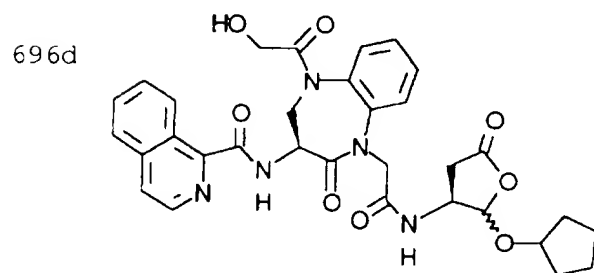
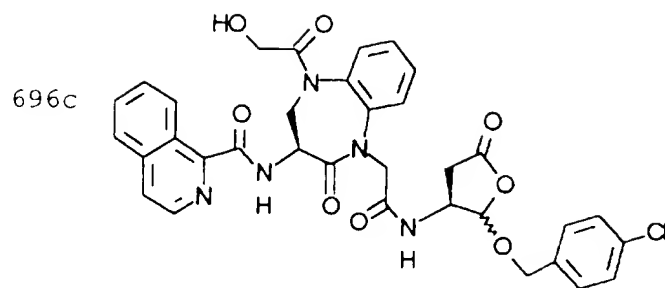




101. The compound according to claim 99,
selected from the group consisting of:



- 899 -



;

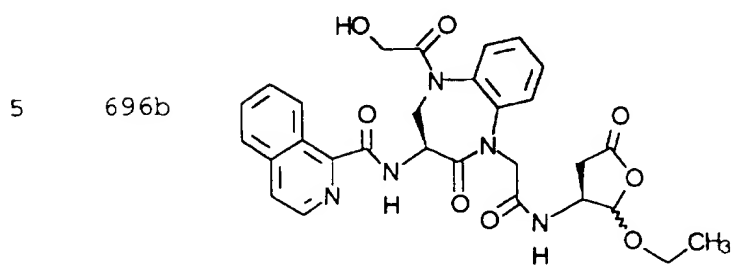
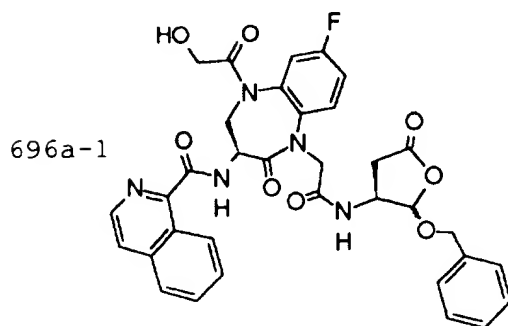
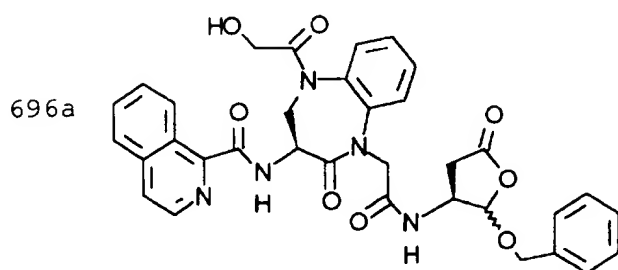
;

;

; and

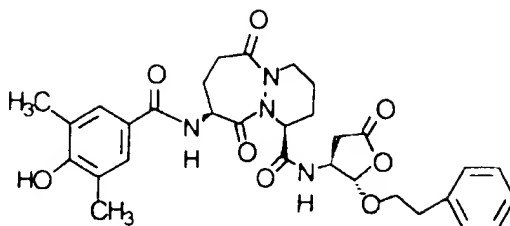
- 898 -

100. The compound according to claim 99
selected from the group consisting of:



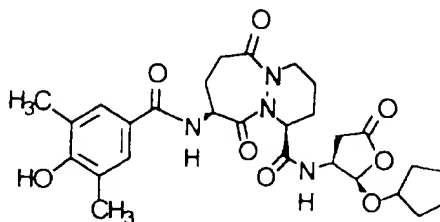
- 897 -

214w-5



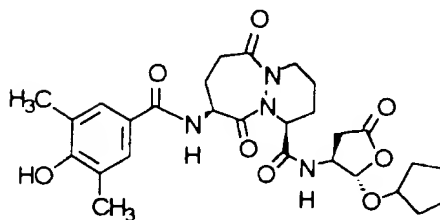
;

214w-6



; and

214w-7



5

98. The compound according to claim 89,
wherein:

10

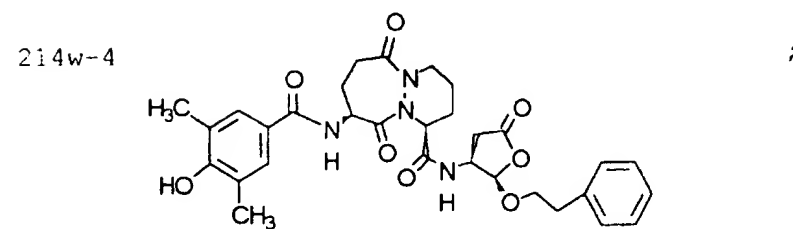
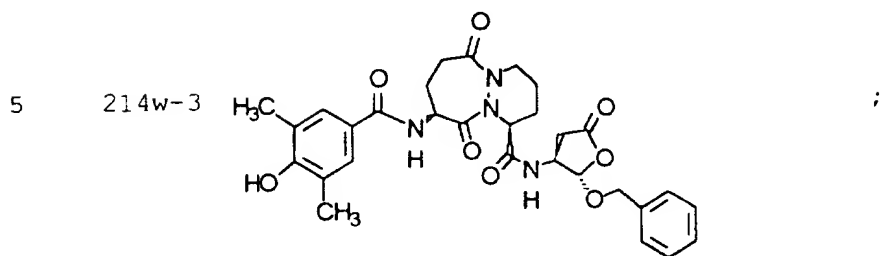
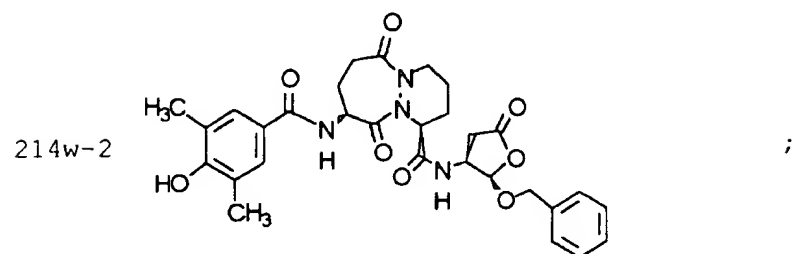
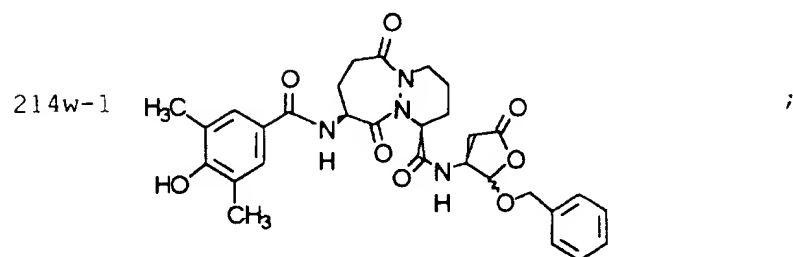
R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

15

99. The compound according to claim 98,
wherein the Ar_3 cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

- 896 -

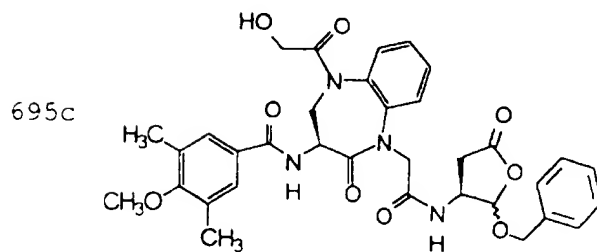
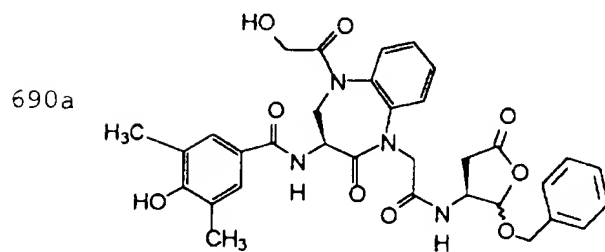
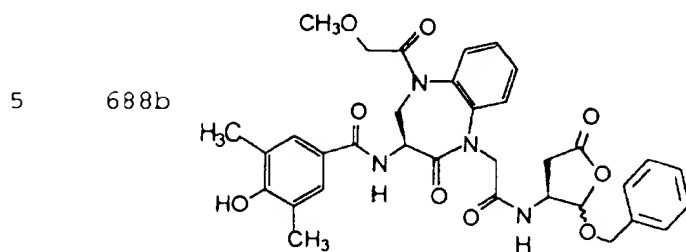
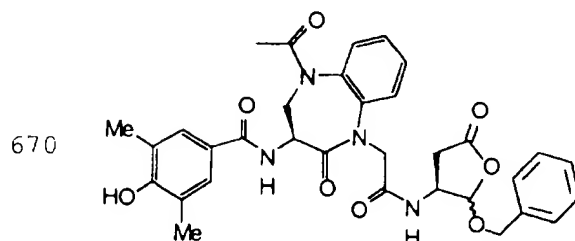
97. The compound according to claim 95,
selected from the group consisting of:



- 895 -

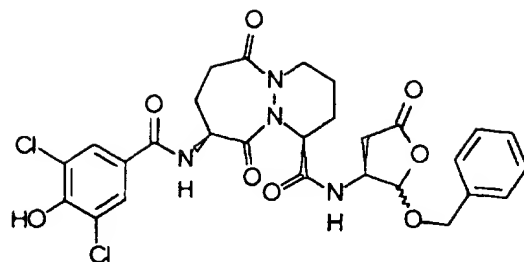
and at the 4-position by $-O-R_5$.

96. The compound according to claim 95,
selected from the group consisting of:



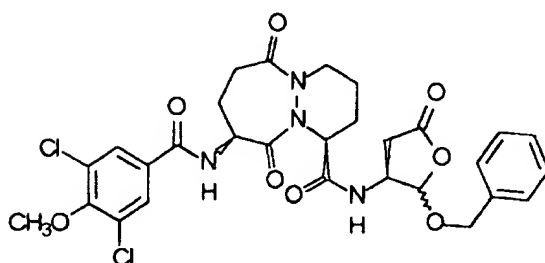
- 894 -

213k



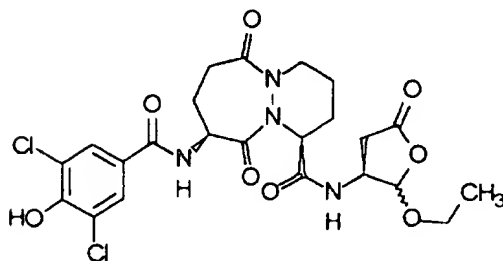
;

213m



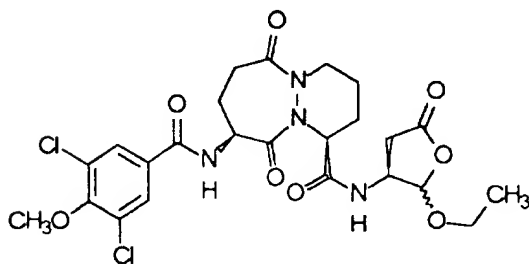
;

550k



; and

550m



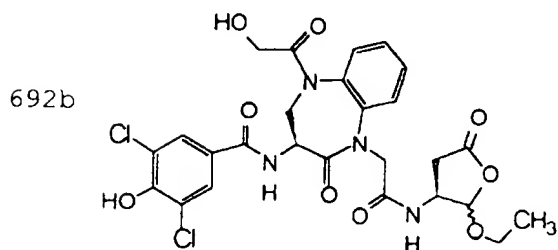
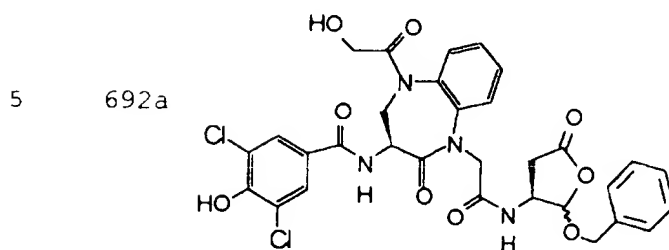
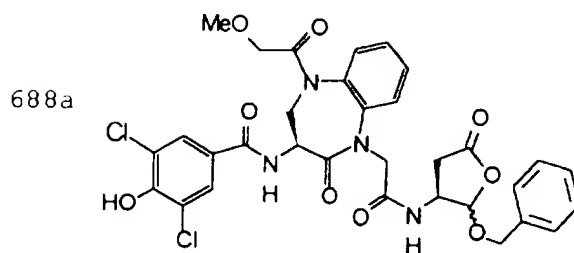
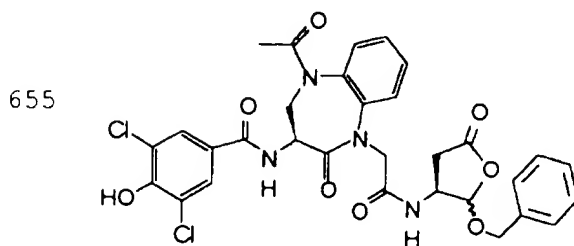
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5

95. The compound according to claim 90, wherein Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by $-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

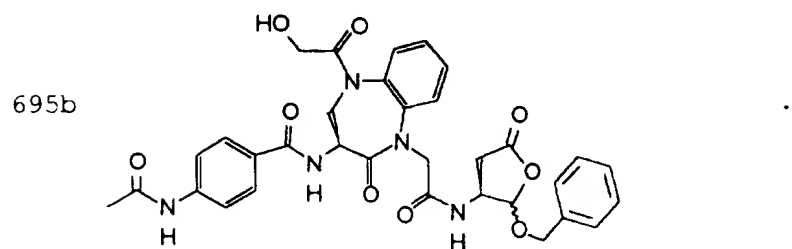
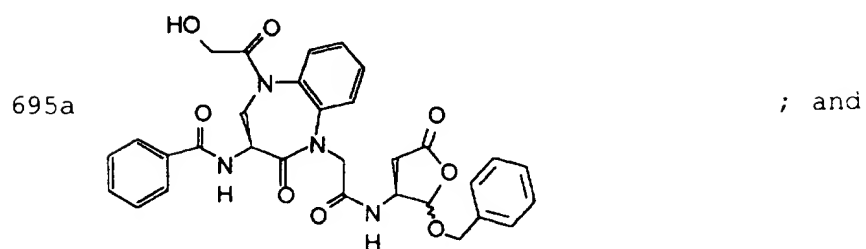
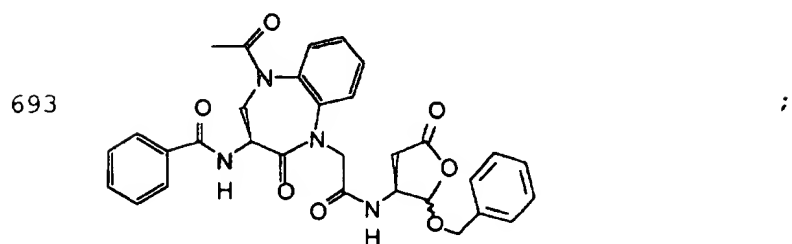
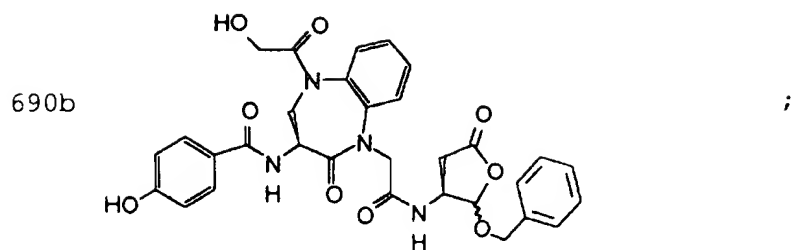
- 893 -

93. The compound according to claim 92,
selected from the group consisting of:



94. The compound according to claim 92,
selected from the group consisting of:

- 892 -



- 5 92. The compound according to claim 90,
 wherein Ar₃ is phenyl being singly or multiply
 substituted at the 3- or 5-position by -Cl or at the 4-
 position by -NH-R₅, -N(R₉)(R₁₀), or -O-R₅.

- 891 -

89. The compound according to claim 88,
wherein R_{10} is Ar_3 .

90. The compound according to claim 89,
wherein:

5 R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3 , wherein the Ar_3
cyclic group is phenyl optionally being singly or
multiply substituted by:

$-R_9$, wherein R_9 is a C_{1-4} straight or branched
alkyl group;

10 $-F$,

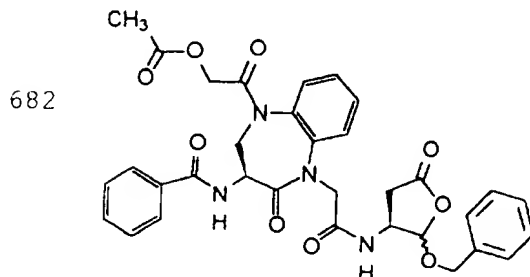
$-Cl$,

$-N(H)-R_5$, wherein $-R_5$ is $-H$ or $-C(O)-R_{10}$, wherein
 R_{10} is a $-C_{1-6}$ straight or branched alkyl group
optionally substituted with $-Ar_3$, wherein Ar_3 is
15 phenyl,

$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a
 $-C_{1-4}$ straight or branched alkyl group, or

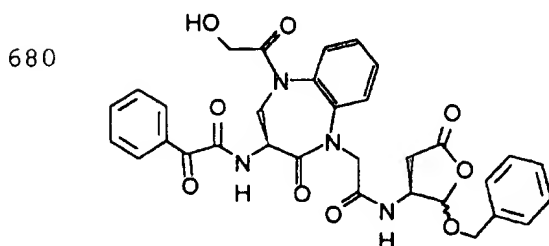
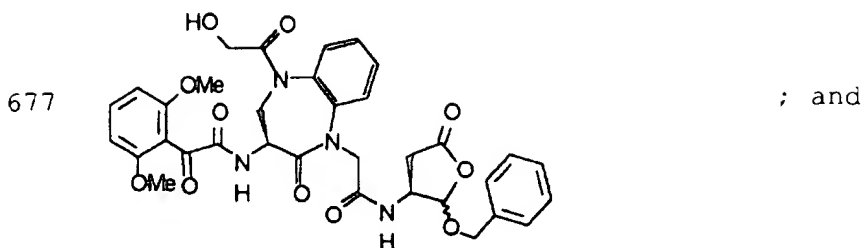
$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or
branched alkyl group.

20 91. The compound according to claim 90,
selected from the group consisting of:



- 890 -

selected from the group consisting of:



84. The compound according to claim 82,
5 wherein R_8 is selected from the group consisting of:

- C(O)- R_{10} ,
- C(O)O- R_9 ,
- C(O)-CH₂-OR₁₀, and
- C(O)-CH₂C(O)- R_9 .

10 85. The compound according to claim 84,
wherein R_8 is -C(O)-CH₂-OR₁₀ and R_{10} is -H or -CH₃.

86. The compound according to claim 81,
wherein R_1 is (e10) and X_5 is CH.

15 87. The compound according to claim 81,
wherein R_1 is (e10) and X_5 is N.

88. The compound according to any one of
claims 80-87 wherein R_5 is -C(O)- R_{10} or -C(O)-C(O)- R_{10} .

- 889 -

optionally substituted with $-\text{Ar}_3$, wherein Ar_3 is phenyl, optionally substituted by $-\text{Q}_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-\text{Q}_1$;

each Q_1 is independently selected from the group consisting of $-\text{NH}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OH}$, $-\text{R}_9$, $-\text{NH}-\text{R}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$ or $-\text{S}(\text{O})_2-\text{R}_9$, $-\text{OR}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$, $-\text{OR}_9$, $-\text{NHR}_9$, and



wherein each R_9 and R_{10} are independently a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with $-\text{Ar}_3$ wherein Ar_3 is phenyl;

provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

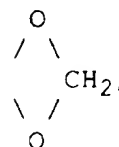
82. The compound according to claim 81, wherein R_1 is (w2).

83. The compound according to claim 82,

- 888 -

consisting of $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{I}$, $-\text{NO}_2$, $-\text{CN}$,
 $=\text{O}$, $-\text{OH}$, $-\text{perfluoro C}_{1-3}$ alkyl, R_5 , $-\text{OR}_5$, $-\text{NHR}_5$, $-\text{OR}_9$,
 $-\text{N}(\text{R}_9)(\text{R}_{10})$, $-\text{R}_9$, $-\text{C}(\text{O})-\text{R}_{10}$, and

5



provided that when $-\text{Ar}_3$ is substituted with a Q_1
 10 group which comprises one or more additional $-\text{Ar}_3$
 groups, said additional $-\text{Ar}_3$ groups are not substituted
 with another $-\text{Ar}_3$.

81. The compound according to claim 80,
 wherein:

15

m is 1;

C is a ring chosen from the set consisting of
 benzo, pyrido, or thieno the ring optionally being
 singly or multiply substituted by halogen, $-\text{NH}_2$,
 $-\text{NH}-\text{R}_5$, $-\text{NH}-\text{R}_9$, $-\text{OR}_{10}$, or $-\text{R}_9$, wherein R_9 is a straight
 20 or branched C_{1-4} alkyl group, and R_{10} is H or a straight
 or branched C_{1-4} alkyl group;

R_6 is H;

R_{13} is H or a C_{1-4} straight or branched alkyl group
 optionally substituted with $-\text{Ar}_3$, $-\text{OH}$, $-\text{OR}_9$, $-\text{CO}_2\text{H}$,
 25 wherein the R_9 is a C_{1-4} branched or straight chain
 alkyl group; wherein Ar_3 is morpholinyl or phenyl,
 wherein the phenyl is optionally substituted by $-\text{Q}_1$;

R_{21} is $-\text{H}$ or $-\text{CH}_3$;

R_{51} is a C_{1-6} straight or branched alkyl group

- 887 -

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3 , and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9 , $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2 , =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group

- 886 -

-S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-O-R₉,
 -C(O)C(O)-R₁₀,
 5 -R₉,
 -H,
 -C(O)C(O)-OR₁₀, and
 -C(O)C(O)-N(R₉)(R₁₀);

10 X₅ is CH or N;

Y₂ is H₂ or O;

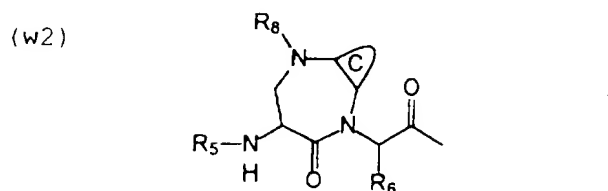
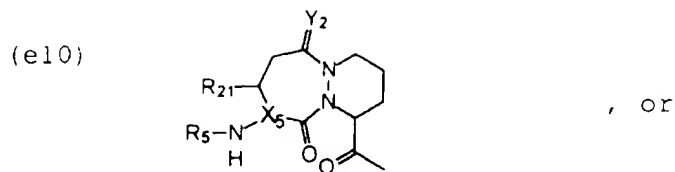
15 R₆ is selected from the group consisting of -H and
 -CH₃;

R₈ is selected from the group consisting of:

-C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-N(H)-R₁₀,
 20 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀;
 -C(O)-CH₂N(R₁₀)(R₁₀),
 25 -C(O)-CH₂C(O)-O-R₉,
 -C(O)-CH₂C(O)-R₉,
 -H, and
 -C(O)-C(O)-OR₁₀;

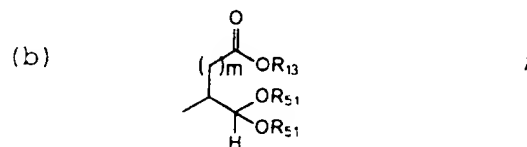
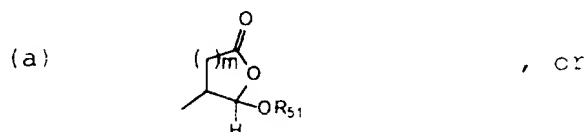
30 each R₉ is independently selected from the group
 consisting of -Ar₃ and a -C₁₋₆ straight or branched
 alkyl group optionally substituted with -Ar₃, wherein
 the -C₁₋₆ alkyl group is optionally unsaturated;

- 885 -



5 C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl; the ring optionally being singly or multiply substituted by $-Q_1$;

10 R_2 is:



m is 1 or 2;

15 each R_5 is independently selected from the group consisting of:

- C(O)- R_{10} ,
- C(O)O- R_9 ,
- C(O)-N(R_{10})(R_{10})

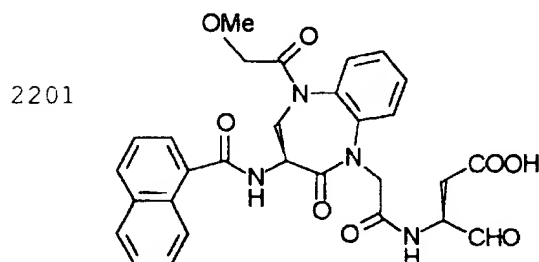
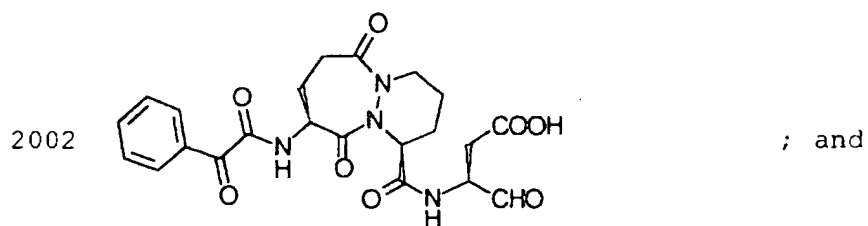
- 884 -

R_3 is $-C(O)-H$; and

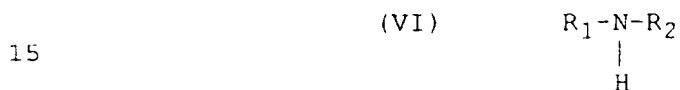
R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is phenyl, substituted by



79. The compound according to claim 68,
10 selected from the group consisting of:



80. A compound represented by the formula:



wherein:

R_1 is:

- 883 -

phenyl,

-N(R₉)(R₁₀), wherein R₉ and R₁₀ are independently a
-C₁₋₄ straight or branched alkyl group, or

5 -O-R₅, wherein R₅ is H or a -C₁₋₄ straight or
branched alkyl group.

75. The compound according to claim 74,
wherein Ar₃ is phenyl being optionally singly or
multiply substituted at the 3- or 5-position by -Cl or
at the 4-position by -NH-R₅, -N(R₉)(R₁₀), or -O-R₅.

10 76. The compound according to claim 68,
wherein:

R₃ is -C(O)-H;

15 R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃
cyclic group is selected from the group consisting of
is indolyl, benzimidazolyl, thienyl, and
benzo[b]thiophenyl, and said cyclic group optionally
being singly or multiply substituted by -Q₁.

77. The compound according to claim 68,
wherein:

20 R₃ is -C(O)-H; and

R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃
cyclic group is selected from quinolyl and isoquinolyl,
and said cyclic group optionally being singly or
multiply substituted by -Q₁.

25 78. The compound according to claim 66,
wherein:

- 882 -

is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl.

5 69. The compound according to claim 68, wherein R_{21} is $-CH_3$.

70. The compound according to claim 68, wherein R_5 is $-C(O)-C(O)-OR_{10}$.

10 71. The compound according to claim 68, wherein R_5 is $-C(O)-C(O)-OR_{10}$ and R_{21} is $-CH_3$.

72. The compound according to any one of claims 66, 67, 70 and 71, wherein R_3 is $-C(O)-H$.

73. The compound according to any one of claims 65, 68 and 69, wherein R_3 is $-C(O)-H$.

15 74. The compound according to claim 68, wherein:

R_3 is $-C(O)-H$, and

R_5 is $-C(O)-R_{10}$, wherein:

20 R_{10} is Ar_3 , wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

$-F$,

$-Cl$,

25 $-N(H)-R_5$, wherein $-R_5$ is $-H$ or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is

- 881 -

4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

5 -C(O)-OR₉, wherein R₉ is isobutyl or -CH₂-Ar₃ and the Ar₃ cyclic group is phenyl;

and when R₁₁ is Ar₄, wherein the Ar₄ cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl or 5-(1-(4-chloro-2-pyridinyl)-3-trifluoromethyl)pyrazolyl, then R₅ cannot be:

10 -C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl;

and when R₁₁ is Ar₄, wherein the Ar₄ cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl, then R₅ cannot be:

15 -C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is 4-(dimethylaminomethyl)phenyl, or

-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl, unsubstituted by -Q₁; and when

20 Y₂ is O, R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁ is -C(O)-Ar₄, wherein the Ar₄ cyclic group is 2,5-dichlorophenyl, then R₅ cannot be:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methylphenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benzotriazolyl, N-carboethoxy-5-benzotriazolyl, N-carboethoxy-5-benzimidazolyl, or

25 -C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl, unsubstituted by -Q₁; and when

30 Y₂ is H₂, R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁

- 880 -

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, R_5 , $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

$$\begin{array}{c} O \\ / \quad \backslash \\ \quad CH_2 \\ \backslash \quad / \\ O \end{array}$$

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

provided that when:

m is 1;
 R_{15} is $-OH$;
 R_{21} is $-H$; and

Y_2 is O and R_3 is $-C(O)-H$, then R_5 cannot be:
 $-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$, 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

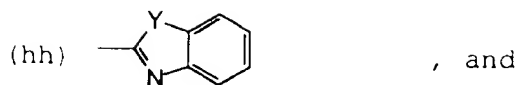
$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

Y_2 is O , R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O , and R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

$-H$;

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl,

- 879 -



wherein each Y is independently selected from the
 5 group consisting of O and S;

each Ar₃ is a cyclic group independently selected
 from the set consisting of an aryl group which contains
 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
 and an aromatic heterocycle group containing between 5
 10 and 15 ring atoms and between 1 and 3 rings, said
 heterocyclic group containing at least one heteroatom
 group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
 -N(R₅)-, and -N(R₉)- said heterocycle group optionally
 containing one or more double bonds, said heterocycle
 15 group optionally comprising one or more aromatic rings,
 and said cyclic group optionally being singly or
 multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected
 from the set consisting of an aryl group which contains
 20 6, 10, 12, or 14 carbon atoms and between 1 and 3
 rings, and a heterocycle group containing between 5 and
 15 ring atoms and between 1 and 3 rings, said
 heterocyclic group containing at least one heteroatom
 group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-,
 25 -N(R₅)-, and -N(R₉)- said heterocycle group optionally
 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic rings,
 and said cyclic group optionally being singly or
 multiply substituted by -Q₁;

- 878 -

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

5 each R_9 is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

10 each R_{10} is independently selected from the group consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

15 each R_{11} is independently selected from the group consisting of:
-Ar₄,
-(CH₂)₁₋₃-Ar₄,
-H, and
-C(O)-Ar₄;

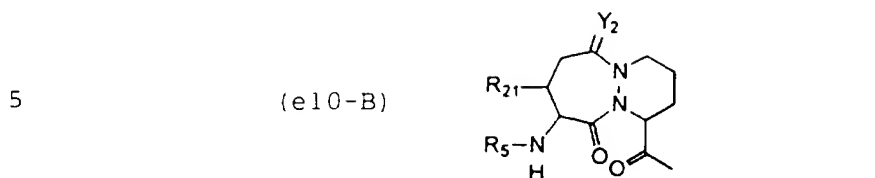
20 R_{15} is selected from the group consisting of -OH, -OAr₃, -N(H)-OH, and -OC₁₋₆, wherein C₁₋₆ is a straight or branched alkyl group optionally substituted with -Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

25 each R_{21} is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ or phenyl, optionally substituted by Q₁:

- 877 -

m is 1 or 2;

R₁ is:R₃ is selected from the group consisting of:

- 10
- CN,
 - C(O)-H,
 - C(O)-CH₂-T₁-R₁₁,
 - C(O)-CH₂-F,
 - C=N-O-R₉, and
 - CO-Ar₂;

15 each R₅ is independently selected from the group consisting of:

- 20
- C(O)-R₁₀,
 - C(O)O-R₉,
 - C(O)-N(R₁₀)(R₁₀)
 - S(O)₂-R₉,
 - S(O)₂-NH-R₁₀,
 - C(O)-CH₂-O-R₉,
 - C(O)C(O)-R₁₀,
 - R₉,
 - H,
 - 25 -C(O)C(O)-OR₁₀, and
 - C(O)C(O)-N(R₉)(R₁₀);

Y₂ is H₂ or O;

- 876 -

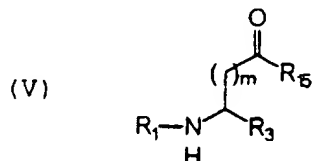
from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said
 5 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,
 10 and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, -OR₉,
 15 -N(R₉)(R₁₀), -R₉, -C(O)-R₁₀, and $\begin{array}{c} \text{O} \\ / \quad \backslash \\ \text{CH}_2 \\ \backslash \quad / \\ \text{O} \end{array}$;

20 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

67. The compound according to claim 66,
 25 wherein R₂₁ is -CH₃.

68. A compound represented by the formula:



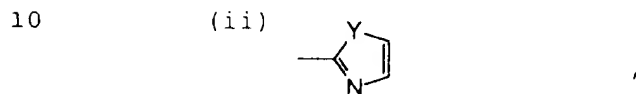
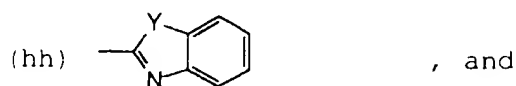
wherein:

- 875 -

$-\text{Ar}_3$, $-\text{CONH}_2$, $-\text{OR}_5$, $-\text{OH}$, $-\text{OR}_9$, or $-\text{CO}_2\text{H}$;

each R_{21} is independently selected from the group consisting of $-\text{H}$ or a $-\text{C}_{1-6}$ straight or branched alkyl group;

5 Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-\text{Q}_1$ or phenyl, optionally substituted by Q_1 :



wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected
 15 from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom
 20 group selected from $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, SO_2 , $=\text{N}-$, and $-\text{NH}-$, $-\text{N}(\text{R}_5)-$, and $-\text{N}(\text{R}_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or
 25 multiply substituted by $-\text{Q}_1$;

each Ar_4 is a cyclic group independently selected

- 874 -

5 -C(O)-H,
 -C(O)-CH₂-T₁-R₁₁,
 -C(O)-CH₂-F,
 -C=N-O-R₉, and
 -CO-Ar₂;

each R₅ is -C(O)C(O)-OR₁₀;

Y₂ is H₂ or O;

10 each T₁ is independently selected from the group
consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

each R₉ is independently selected from the group
consisting of -Ar₃ and a -C₁₋₆ straight or branched
alkyl group optionally substituted with -Ar₃, wherein
the -C₁₋₆ alkyl group is optionally unsaturated;

15 each R₁₀ is independently selected from the group
consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a
-C₁₋₆ straight or branched alkyl group optionally
substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is
optionally unsaturated;

20 each R₁₁ is independently selected from the group
consisting of:

 -Ar₄,
 -(CH₂)₁₋₃-Ar₄,
 -H, and
25 -C(O)-Ar₄;

R₁₅ is selected from the group consisting of -OH,
-OAr₃, -N(H)-OH, and -OC₁₋₆, wherein C₁₋₆ is a straight
or branched alkyl group optionally substituted with

- 873 -

containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

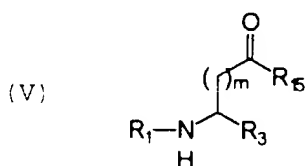
5 each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, -perfluoro C_{1-3} alkyl, R_5 , $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

10 $\begin{array}{c} O \\ / \quad \backslash \\ \quad CH_2 \\ \backslash \quad / \\ O \end{array}$;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

15

66. A compound represented by the formula:

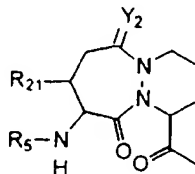


wherein:

20 m is 1 or 2;

R_1 is:

(e10-B)

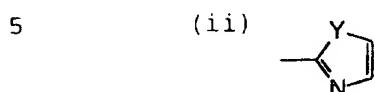
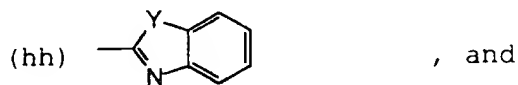


;

25 R_3 is selected from the group consisting of:
 $-CN$,

- 872 -

group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1 :

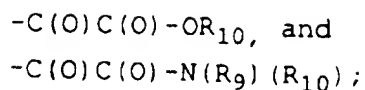


wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, $-NH-$, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally

- 871 -



Y_2 is H_2 or O ;

5 each T_1 is independently selected from the group consisting of $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, and $-\text{S}(\text{O})_2-$;

10 each R_9 is independently selected from the group consisting of $-\text{Ar}_3$ and a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, wherein the $-\text{C}_{1-6}$ alkyl group is optionally unsaturated;

15 each R_{10} is independently selected from the group consisting of $-\text{H}$, $-\text{Ar}_3$, a $-\text{C}_{3-6}$ cycloalkyl group, and a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, wherein the $-\text{C}_{1-6}$ alkyl group is optionally unsaturated;

 each R_{11} is independently selected from the group consisting of:

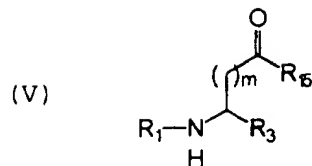
20 $-\text{Ar}_4$,
 $-(\text{CH}_2)_{1-3}-\text{Ar}_4$,
 $-\text{H}$, and
 $-\text{C}(\text{O})-\text{Ar}_4$;

25 R_{15} is selected from the group consisting of $-\text{OH}$, $-\text{OAr}_3$, $-\text{N}(\text{H})-\text{OH}$, and $-\text{OC}_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, $-\text{CONH}_2$, $-\text{OR}_5$, $-\text{OH}$, $-\text{OR}_9$, or $-\text{CO}_2\text{H}$;

R_{21} is $-\text{CH}_3$;

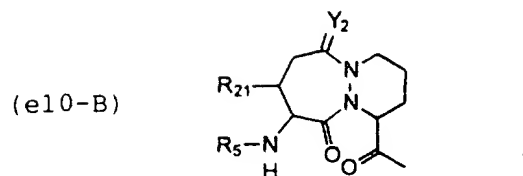
Ar_2 is independently selected from the following

- 870 -



wherein:

m is 1 or 2;

5 R_1 is: R_3 is selected from the group consisting of:

- 10 -CN,
 -C(O)-H,
 -C(O)-CH₂-T₁-R₁₁,
 -C(O)-CH₂-F,
 -C=N-O-R₉, and
 15 -CO-Ar₂;

each R_5 is independently selected from the group
 consisting of:

- C(O)-R₁₀,
 -C(O)O-R₉,
 20 -C(O)-N(R₁₀)(R₁₀)
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-O-R₉,
 -C(O)C(O)-R₁₀,
 25 -R₉,
 -H,

- 869 -

from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said

5 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,

10 and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, -OR₉,

15 -N(R₉)(R₁₀), -R₉, -C(O)-R₁₀, and

$$\begin{array}{c} \text{O} \\ / \quad \backslash \\ \quad \text{CH}_2; \\ \backslash \quad / \\ \text{O} \end{array}$$

20 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

63. The compound according to claim 62,

25 wherein R₁ is (w2).

64. The compound according to claim 62, wherein R₁ is (e10-A).

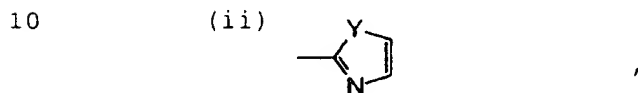
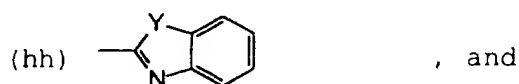
65. A compound represented by the formula:

- 868 -

-Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

each R₂₁ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

- 5 Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ or phenyl, optionally substituted by Q₁:



wherein each Y is independently selected from the group consisting of O and S;

- each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected

- 867 -

-C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-NH-R₁₀,
 -S(O)₂-R₉,
 5 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀,
 -C(O)-CH₂-N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 10 -C(O)-CH₂C(O)-R₉,
 -H, and
 -C(O)-C(O)-OR₁₀;

each R₉ is independently selected from the group
 consisting of -Ar₃ and a -C₁₋₆ straight or branched
 15 alkyl group optionally substituted with -Ar₃, wherein
 the -C₁₋₆ alkyl group is optionally unsaturated;

each R₁₀ is independently selected from the group
 consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a
 -C₁₋₆ straight or branched alkyl group optionally
 20 substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is
 optionally unsaturated;

each R₁₁ is independently selected from the group
 consisting of:

-Ar₄,
 25 -(CH₂)₁₋₃-Ar₄,
 -H, and
 -C(O)-Ar₄;

R₁₅ is selected from the group consisting of -OH,
 -OAr₃, -N(H)-OH, and -OC₁₋₆, wherein C₁₋₆ is a straight
 30 or branched alkyl group optionally substituted with

- 866 -

cyclopentyl, and cyclohexyl;

R_3 is selected from the group consisting of:

- CN,
- C(O)-H,
- 5 -C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

each R_5 is independently selected from the group
10 consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- S(O)₂-R₉,
- 15 -S(O)₂-NH-R₁₀,
- C(O)-CH₂-O-R₉,
- C(O)C(O)-R₁₀,
- R₉,
- H,
- 20 -C(O)C(O)-OR₁₀, and
- C(O)C(O)-N(R₉)(R₁₀);

Y_2 is H₂ or O;

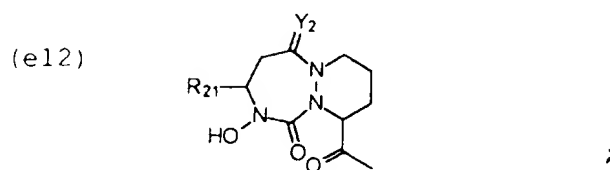
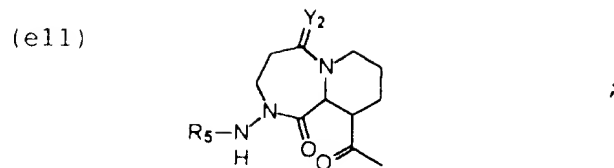
X_7 is -N(R₈)- or -O-;

25 each T₁ is independently selected from the group
consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

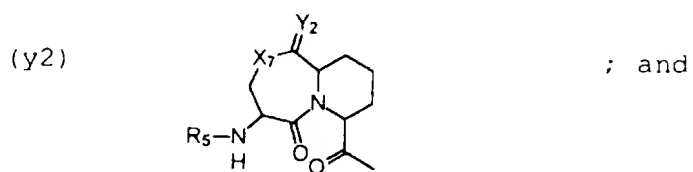
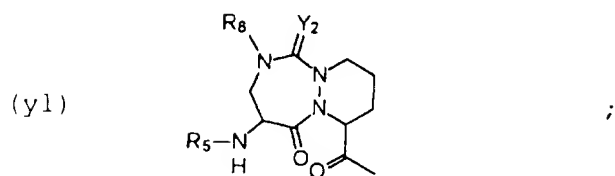
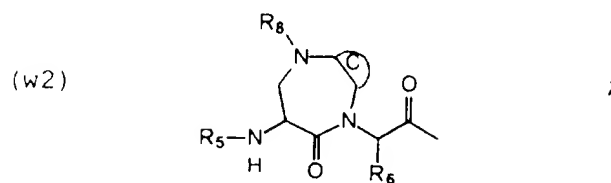
R_6 is selected from the group consisting of -H and
-CH₃;

30 R_8 is selected from the group consisting of:

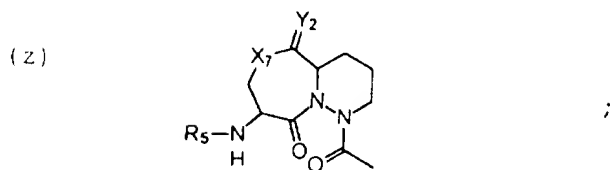
- 865 -



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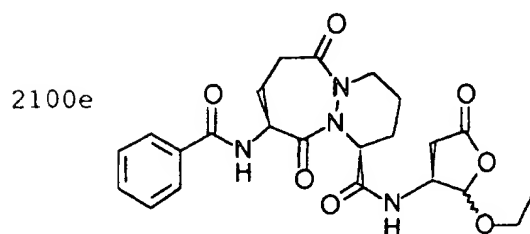
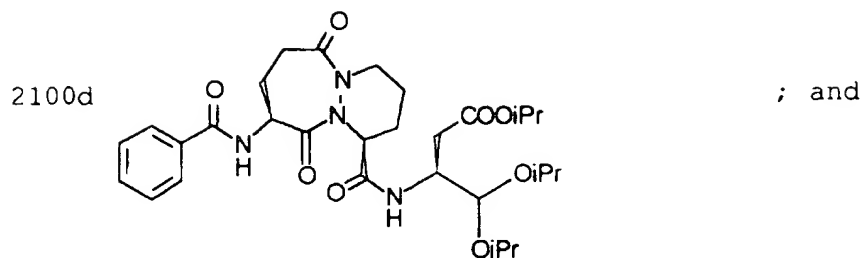


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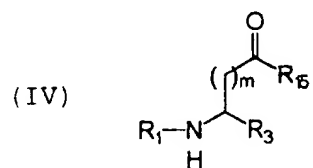


ring C is chosen from the group consisting of
 15 benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,

- 864 -



62. A compound represented by the formula:

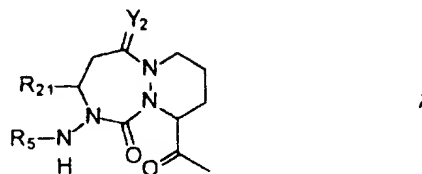


5 wherein:

m is 1 or 2;

R₁ is selected from the group consisting of the following formulae:

10 (e10-A)

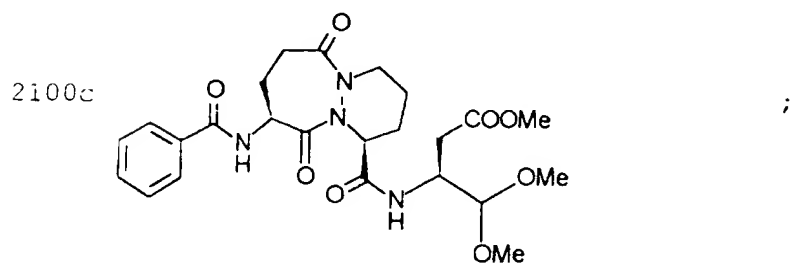
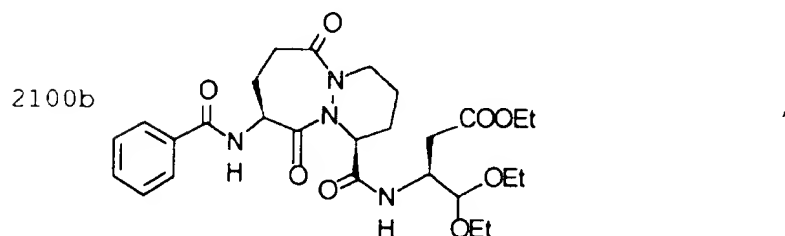
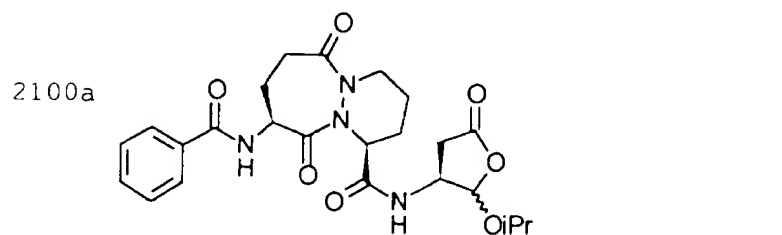
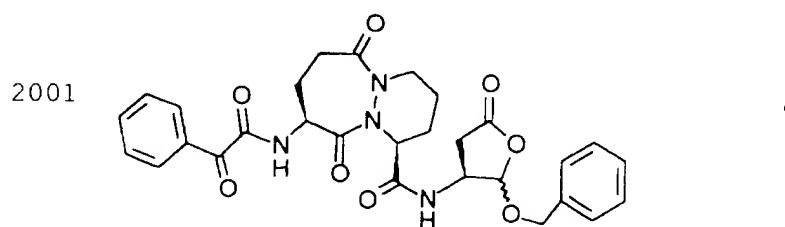


- 863 -

wherein R_1 is (e10) and X_5 is CH.

60. The compound according to claim 57,
wherein R_1 is (e10) and X_5 is N.

61. The compound according to claim 57,
5 selected from the group consisting of:

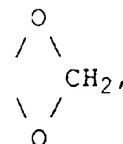


- 862 -

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2 , =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5 , $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and



provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

58. The compound according to claim 57, wherein R_1 is (w2).

59. The compound according to claim 57,

- 861 -

R₈ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(H)-R₁₀,
- 5 -S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-CH₂-OR₁₀,
- C(O)C(O)-R₁₀;
- C(O)-CH₂N(R₁₀)(R₁₀),
- 10 -C(O)-CH₂C(O)-O-R₉,
- C(O)-CH₂C(O)-R₉,
- H, and
- C(O)-C(O)-OR₁₀;

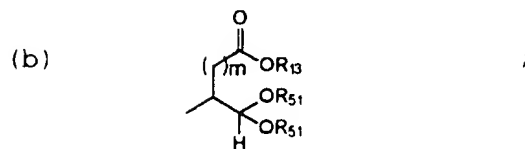
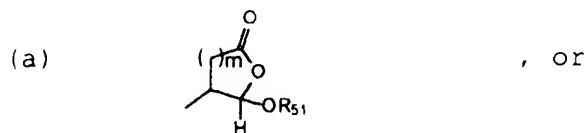
15 each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

20 each R₁₀ is independently selected from the group consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

25 R₁₃ is selected from the group consisting of H, Ar₃, and a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

30 each R₅₁ is independently selected from the group consisting of R₉, -C(O)-R₉, -C(O)-N(H)-R₉, or each R₅₁ taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

- 860 -



m is 1 or 2;

5 each R₅ is independently selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- 10 -S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-CH₂-O-R₉,
- C(O)C(O)-R₁₀,
- R₉,
- 15 -H,
- C(O)C(O)-OR₁₀, and
- C(O)C(O)-N(R₉)(R₁₀);

X₅ is CH or N;

20

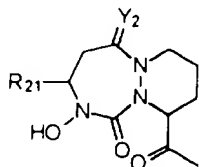
Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

R₆ is selected from the group consisting of -H and
 25 -CH₃;

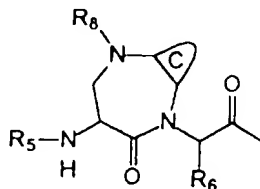
- 859 -

(e12)



;

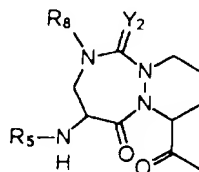
(w2)



;

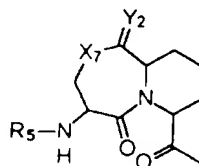
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(y1)



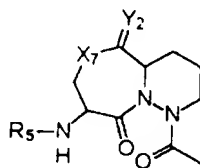
;

(y2)



;

(z)



; and

10

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R₂ is:

- 858 -

atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke in a patient comprising the step of administering to said patient a pharmaceutical composition according to any one of

5 claims 42 to 54.

56. The method according to claim 55, wherein the disease is selected from the group consisting of osteoarthritis, acute pancreatitis,

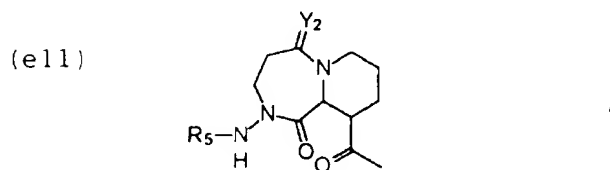
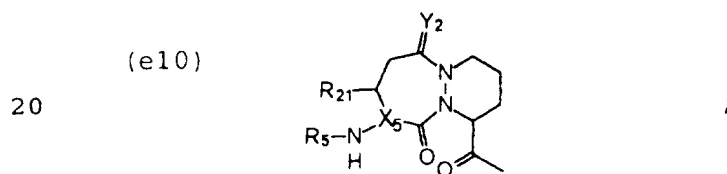
10 rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, psoriasis, and Alzheimer's disease.

57. A compound represented by the formula:



wherein:

R_1 is selected from the group consisting of the following formulae:



- 857 -

to claim 43, wherein the apoptosis-mediated disease is a degenerative disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

54. A pharmaceutical composition for inhibiting an ICE-mediated function comprising an ICE inhibitor according to any one of claims 1-41 and 57-135 and a pharmaceutically acceptable carrier.

55. A method for treating or preventing a disease selected from the group consisting of an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a necrotic disease, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular

- 856 -

47. The pharmaceutical composition according to claim 46, wherein the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, or Crohn's disease, or psoriasis.

5 48. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a destructive bone disorder selected from the group consisting of osteoporosis or multiple myeloma-related bone disorder.

10 49. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a proliferative disorder selected from the group consisting of acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's
15 sarcoma, and multiple myeloma.

50. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an infectious disease, selected from the group consisting of sepsis, septic shock, and Shigellosis.

20 51. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a degenerative or necrotic disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia.

25 52. The pharmaceutical composition according to claim 51, wherein the degenerative disease is Alzheimer's disease.

53. The pharmaceutical composition according

- 855 -

an ICE inhibitor according to any one of claims 1-41 and 57-135 in an amount effective for treating or preventing an IL-1-mediated disease and a pharmaceutically acceptable carrier.

5 43. A pharmaceutical composition comprising an ICE inhibitor according to any one of claims 1-41 and 57-135 in an amount effective for treating or preventing an apoptosis-mediated disease and a pharmaceutically acceptable carrier.

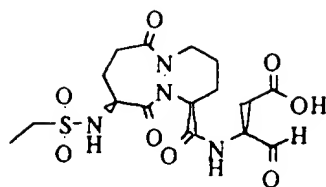
10 44. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an inflammatory disease selected from the group consisting of osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, and adult respiratory distress
15 syndrome.

45. The pharmaceutical composition according to claim 44, wherein the inflammatory disease is osteoarthritis or acute pancreatitis.

20 46. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an autoimmune disease selected from the group consisting of glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-
25 dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, and graft vs host disease.

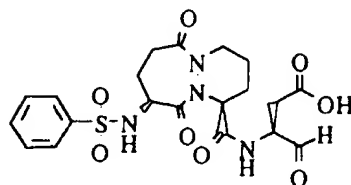
- 854 -

421



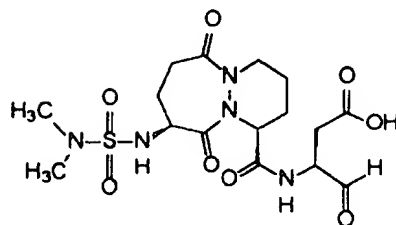
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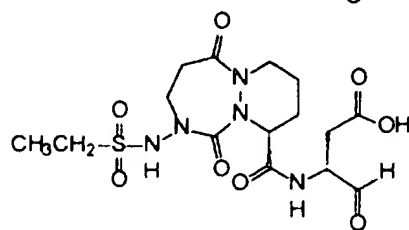
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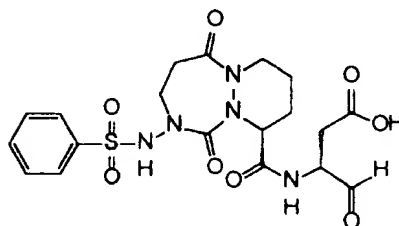
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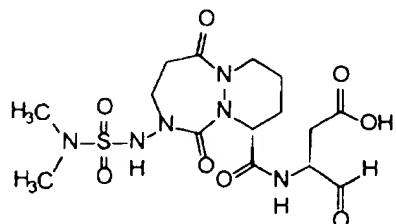
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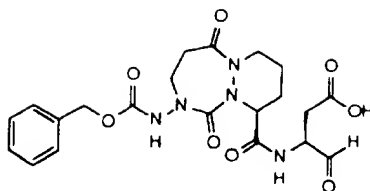


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42. A pharmaceutical composition comprising

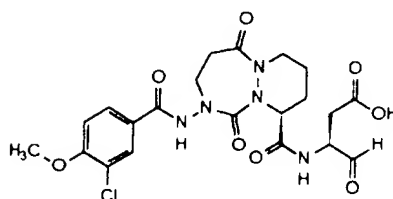
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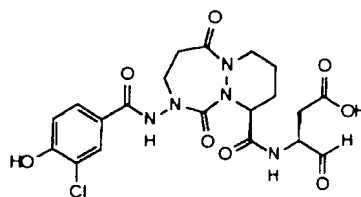


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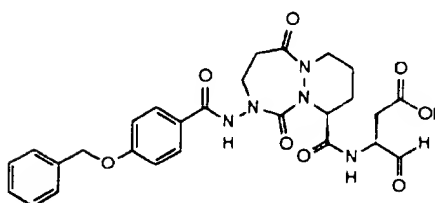


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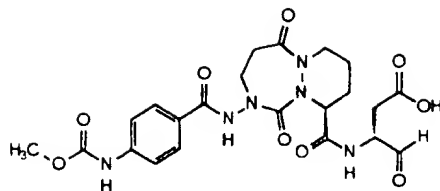
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41. The compound according to claim 33 selected from the group consisting of:

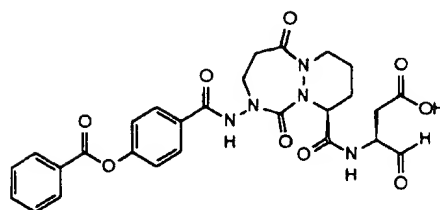
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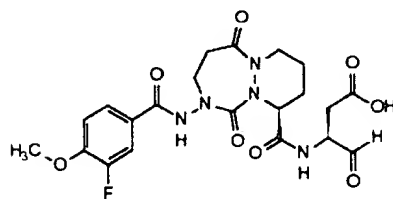
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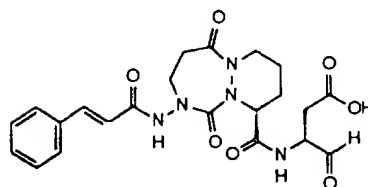
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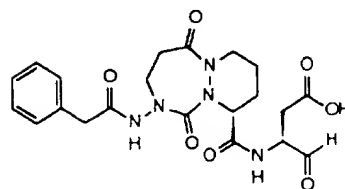
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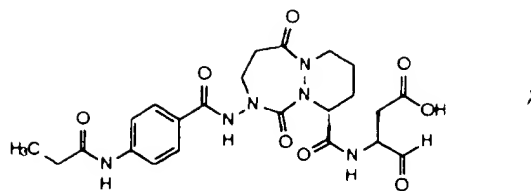
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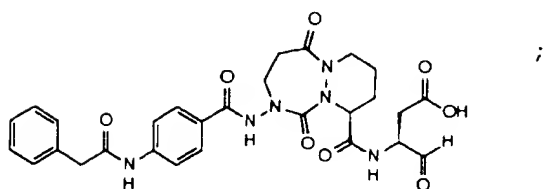
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- 851 -

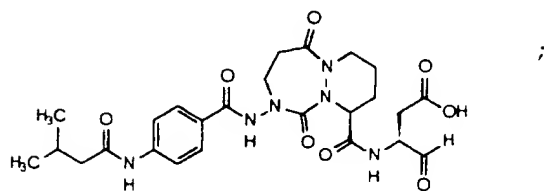
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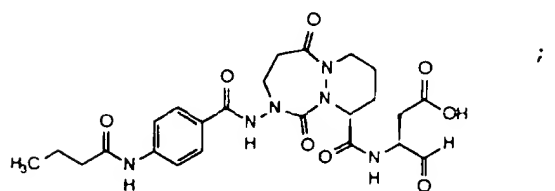
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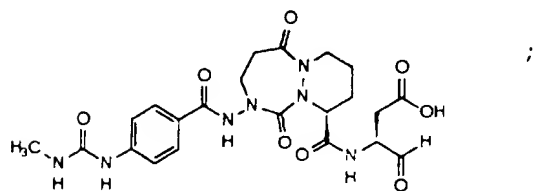


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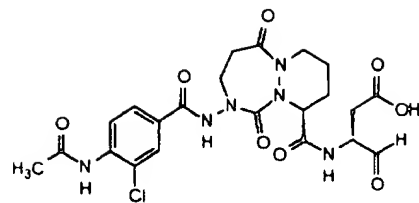
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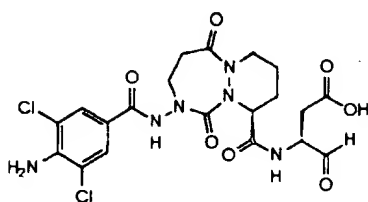
- 850 -

1081s



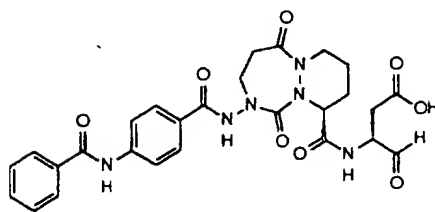
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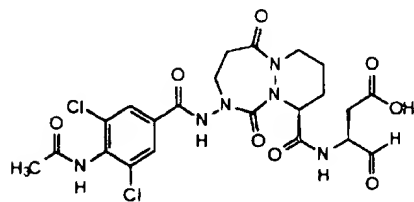
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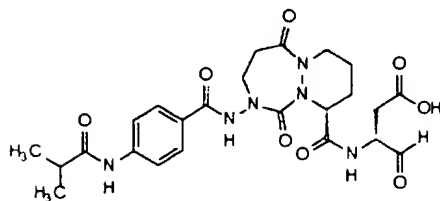
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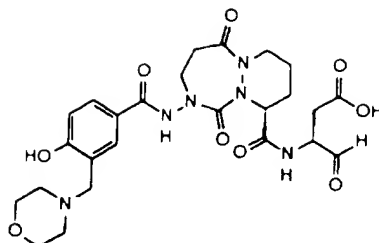
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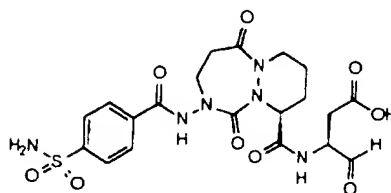
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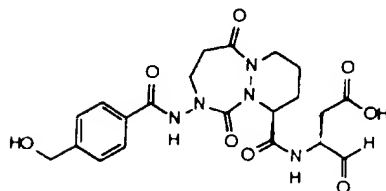
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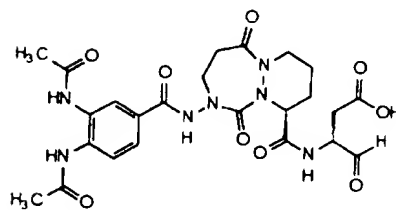
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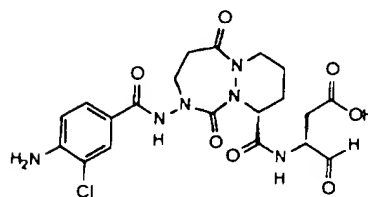
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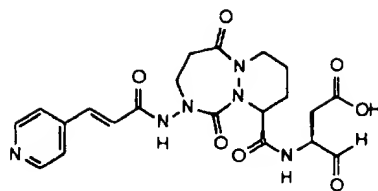
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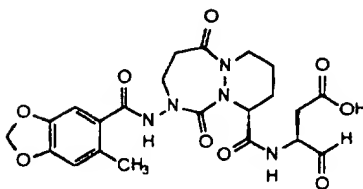
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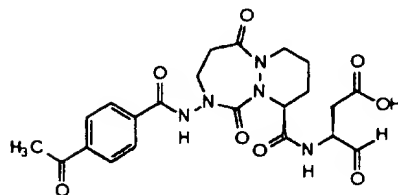
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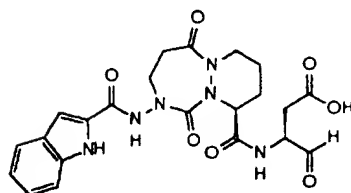
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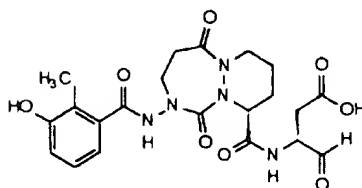


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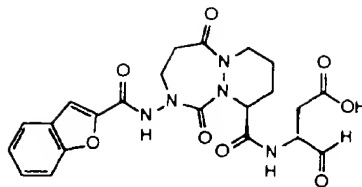
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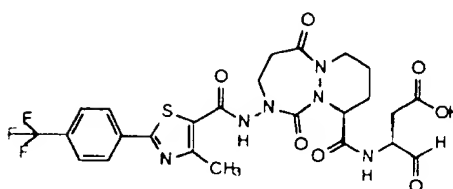


- 847 -

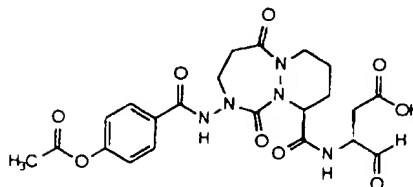
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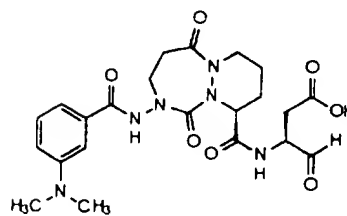
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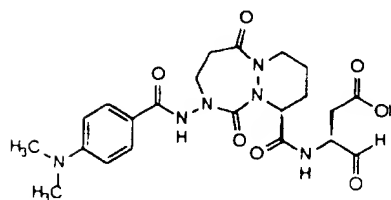


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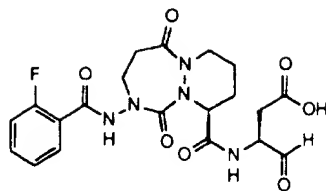
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1071



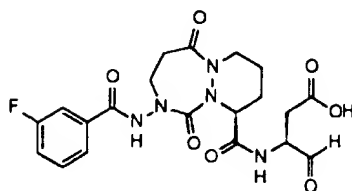
- 846 -

1061



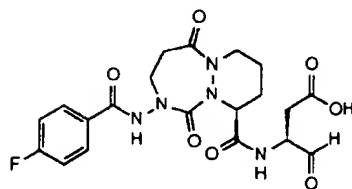
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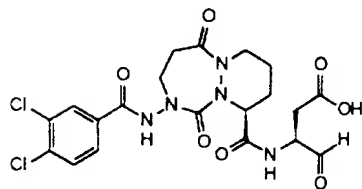
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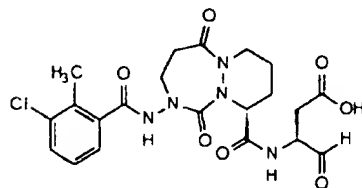
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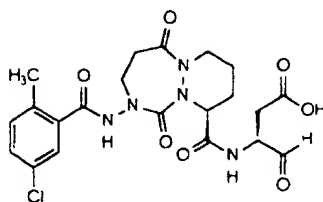
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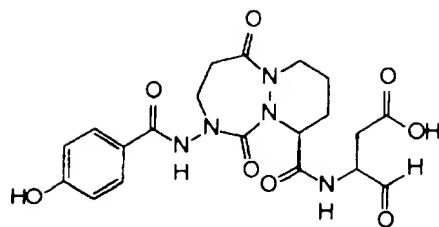
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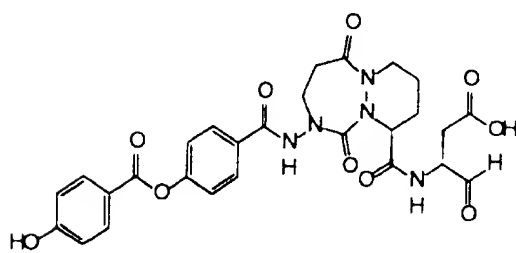
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- 845 -

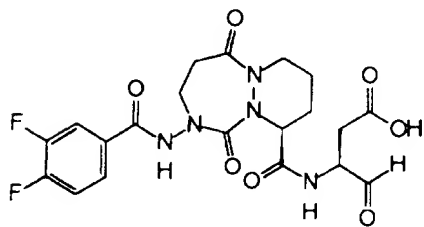
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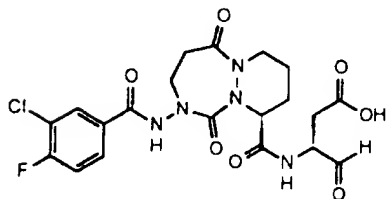
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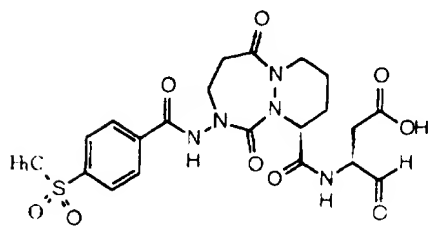


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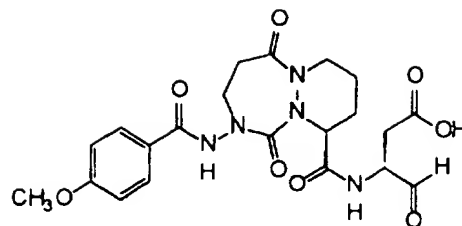
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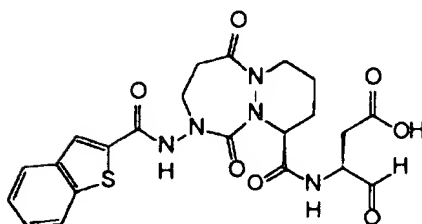


- 844 -

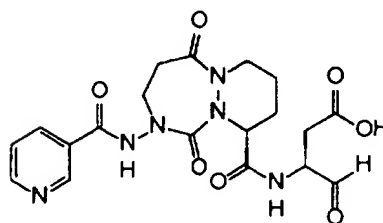
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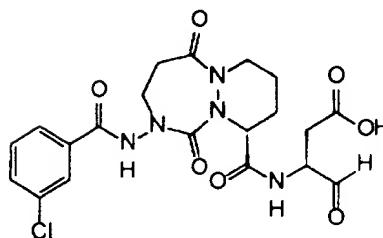
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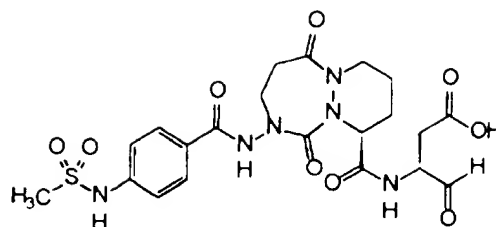


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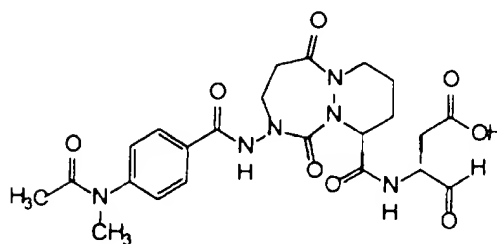


- 843 -

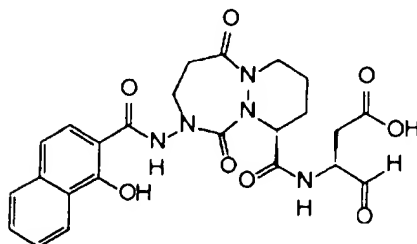
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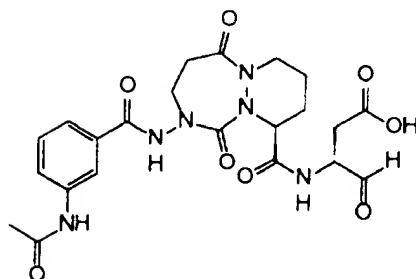
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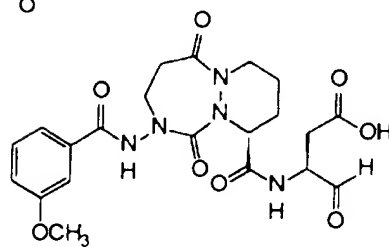


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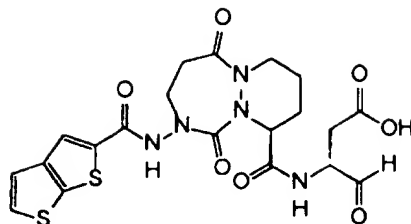
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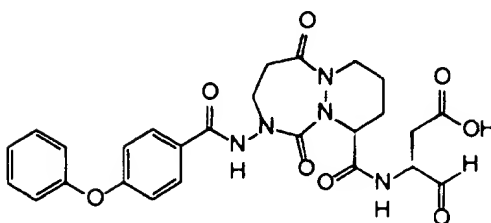
- 842 -

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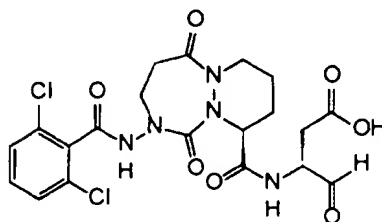
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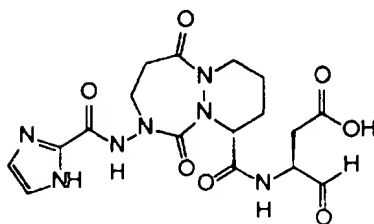
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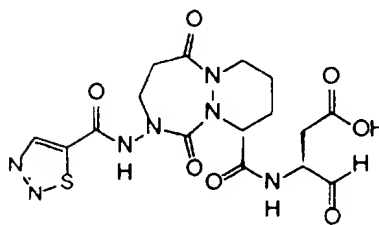
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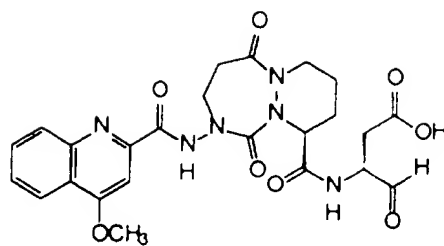
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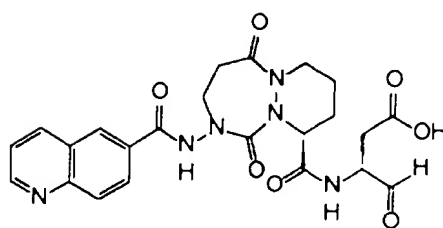
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- 841 -

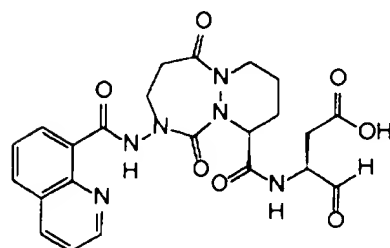
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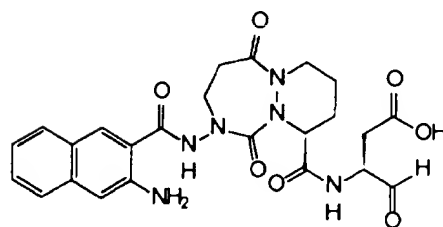
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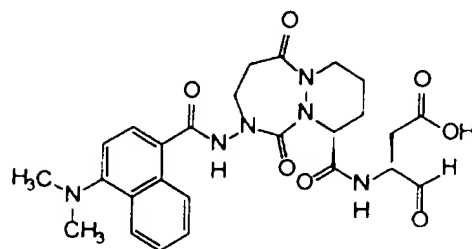


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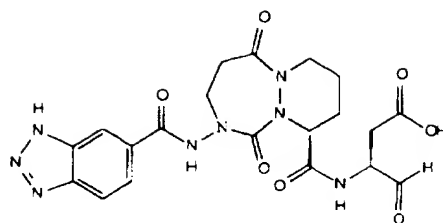
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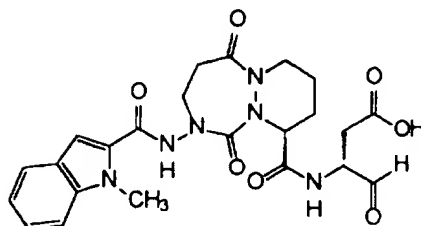
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1032



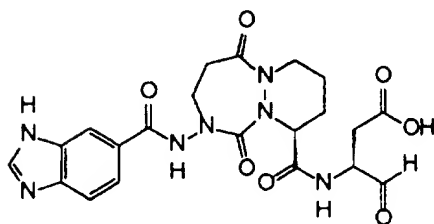
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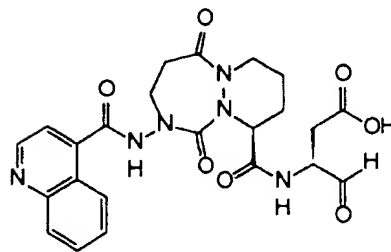
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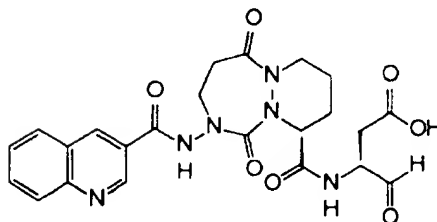
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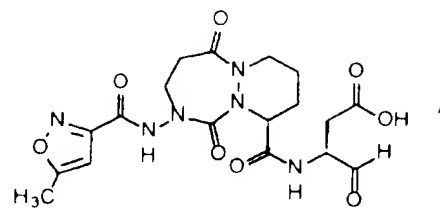
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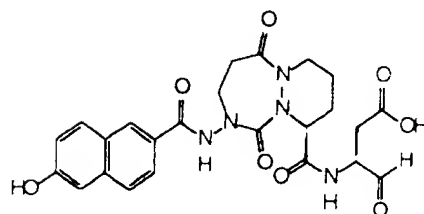
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- 839 -

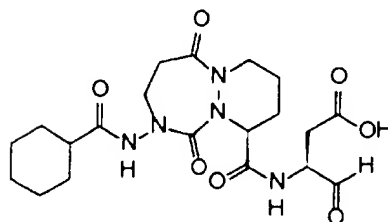
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1025

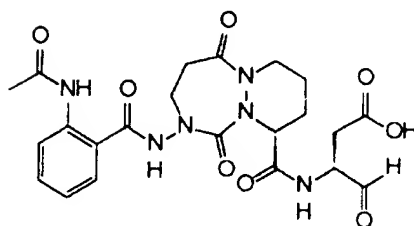


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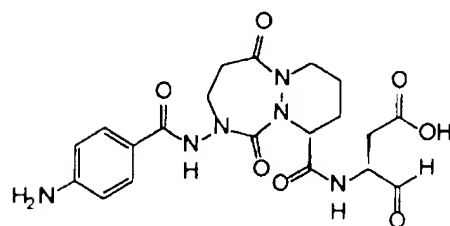


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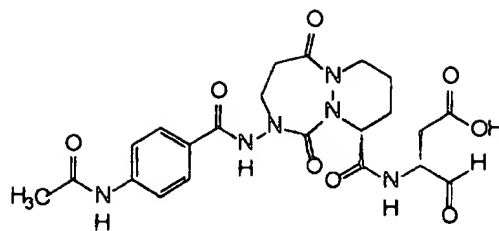


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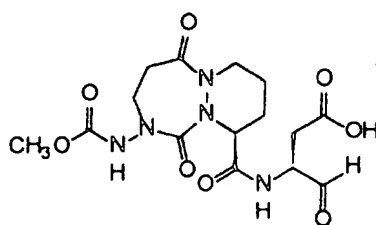


- 838 -

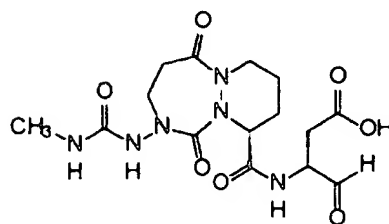
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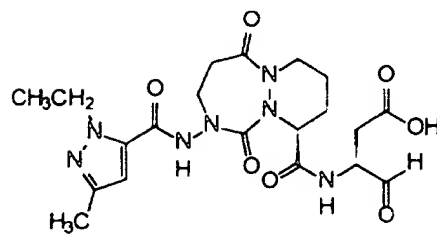
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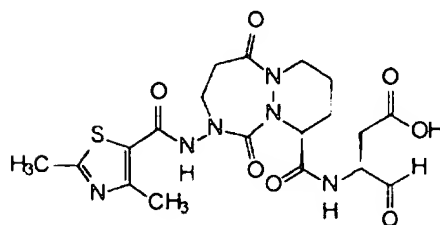


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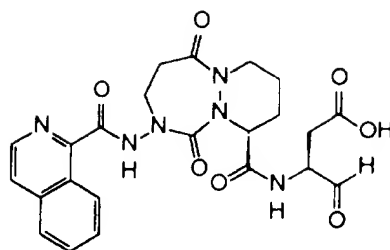
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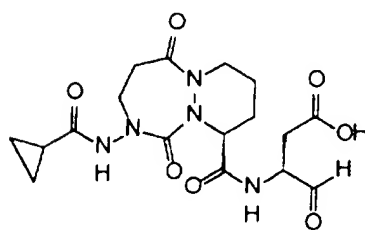
- 837 -

1012



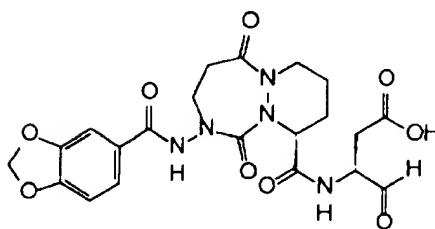
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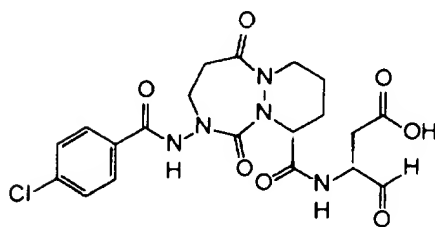
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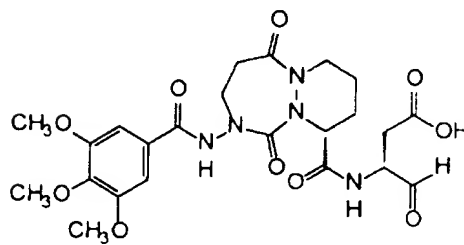
1016



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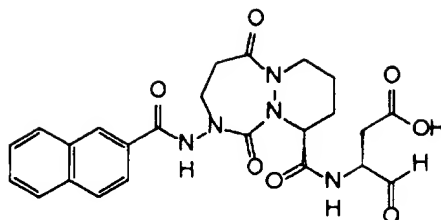
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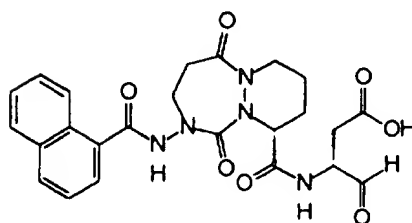
- 836 -

1007



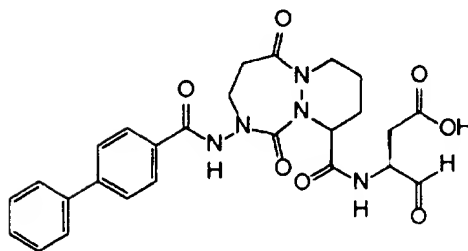
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1008



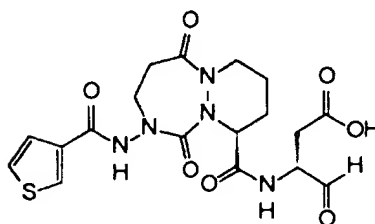
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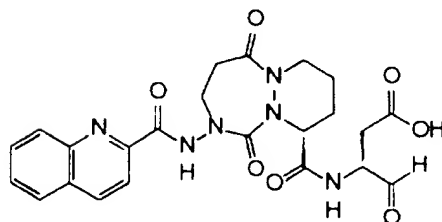
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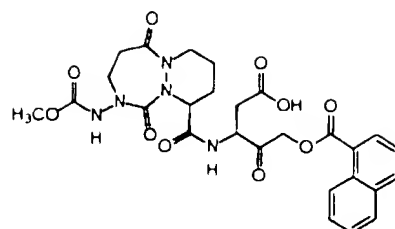
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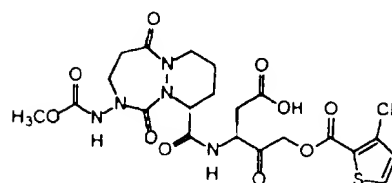
- 835 -

886



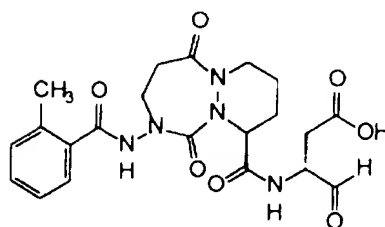
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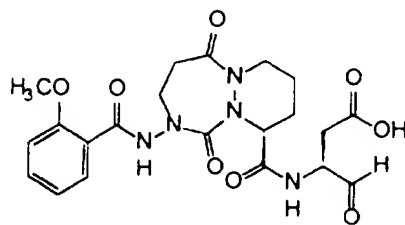
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1004



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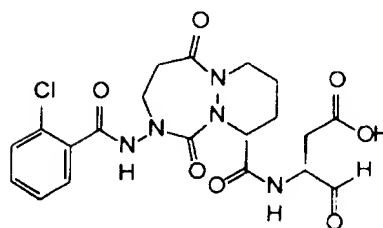
1005



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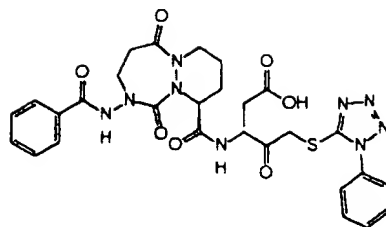
1006



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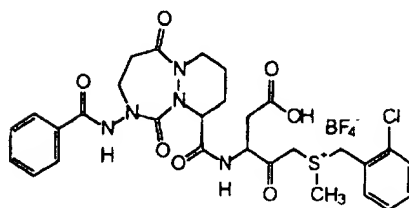
- 834 -

880



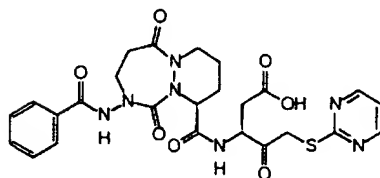
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881



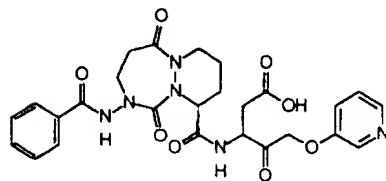
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882



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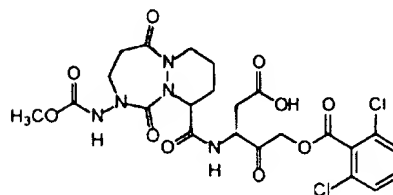
883



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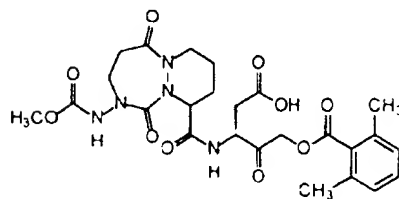
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884



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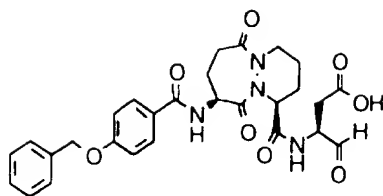
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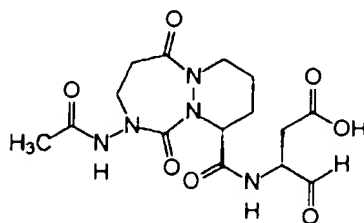
- 833 -

499



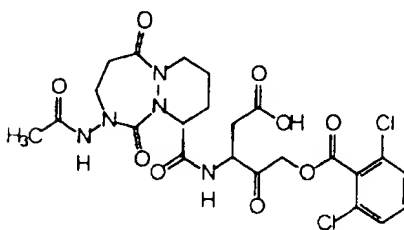
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814C



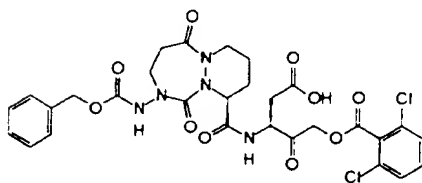
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817C



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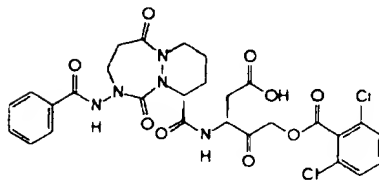
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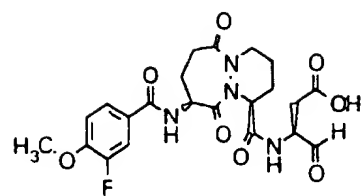
817e



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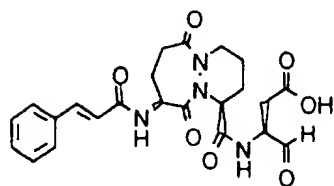
- 832 -

493



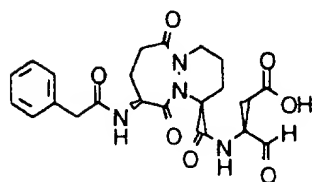
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494



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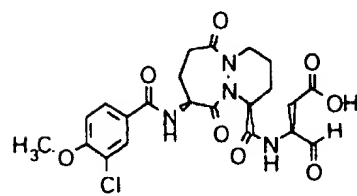
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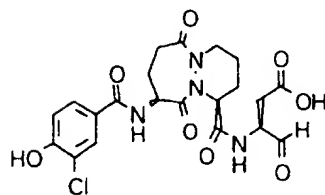
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497



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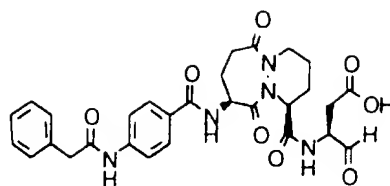
498



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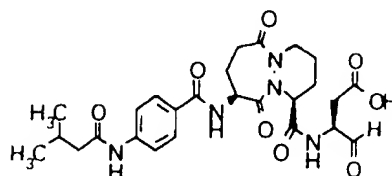
- 831 -

486



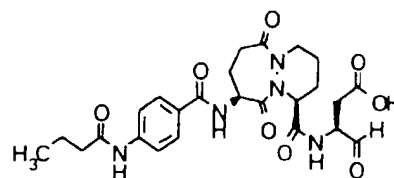
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487



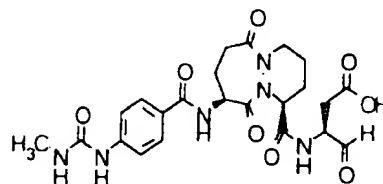
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488



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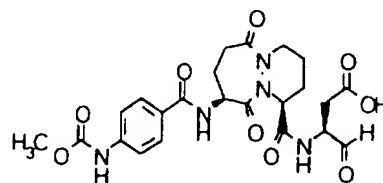
489



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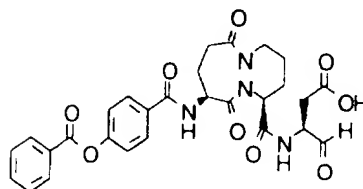
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490



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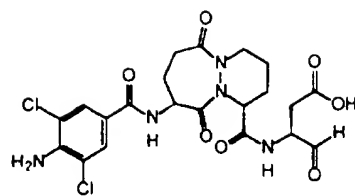
491



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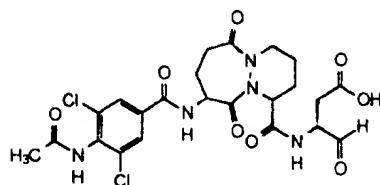
- 830 -

482



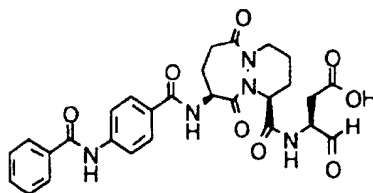
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482s



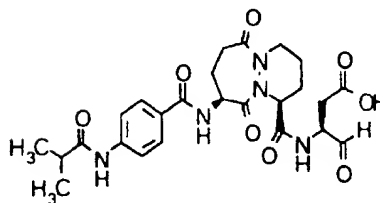
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483



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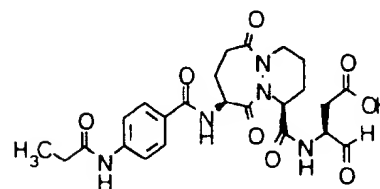
484



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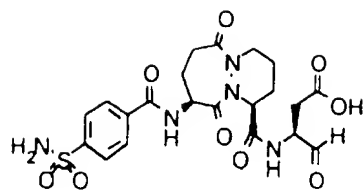
485



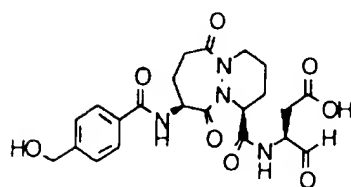
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- 829 -

478

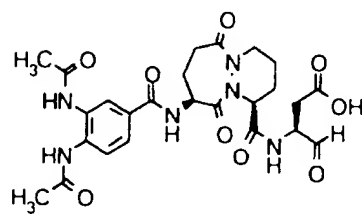


479



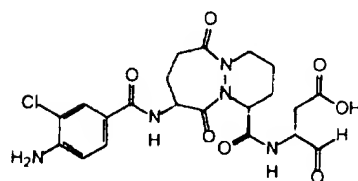
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480



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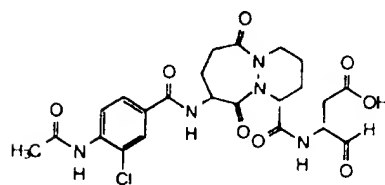
481



2

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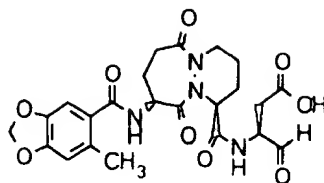
4815



i

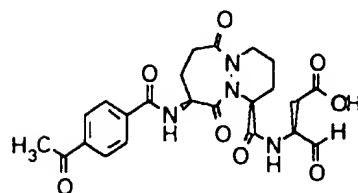
- 828 -

473



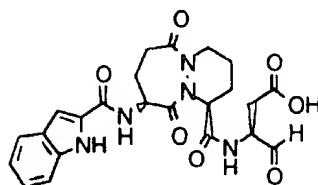
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474



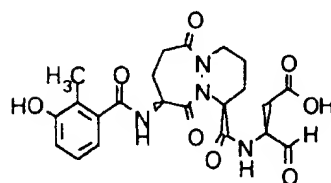
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475



;

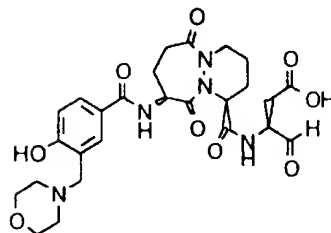
476



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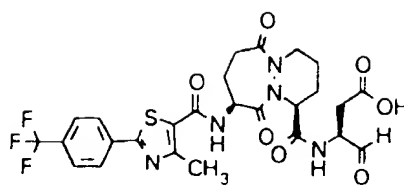
477



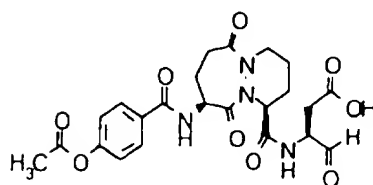
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- 827 -

468

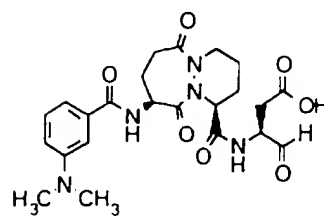


469



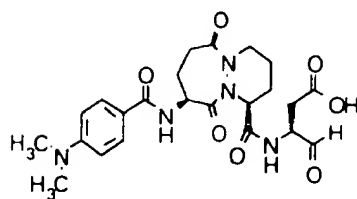
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470



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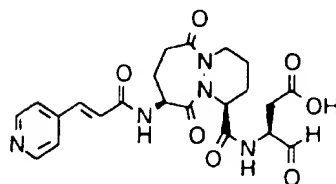
471



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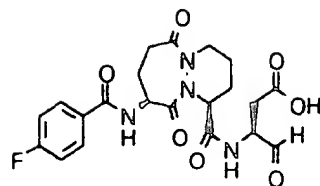
472



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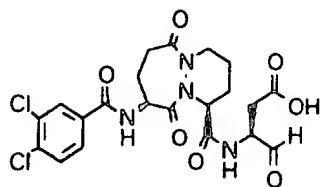
- 826 -

463



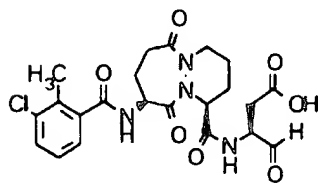
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464



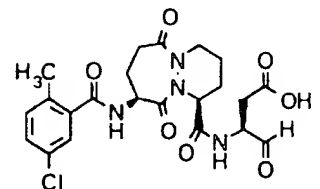
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465



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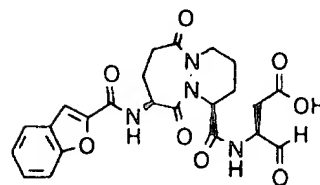
466



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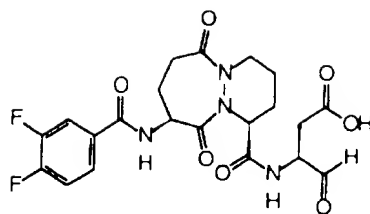
467



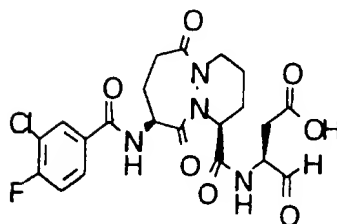
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- 825 -

458

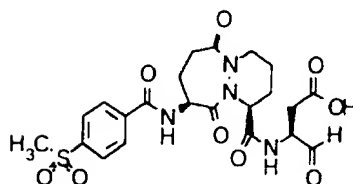


459



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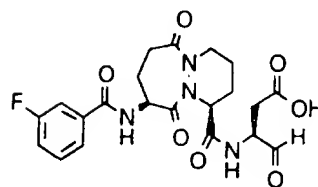
460



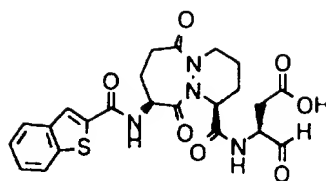
i

5

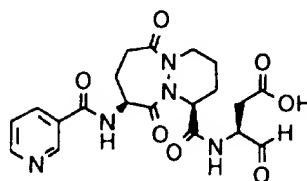
462



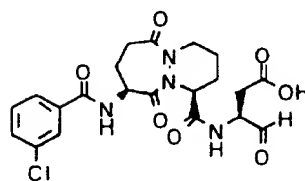
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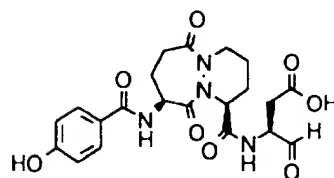
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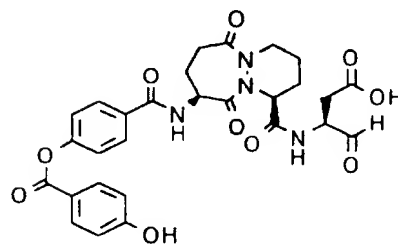
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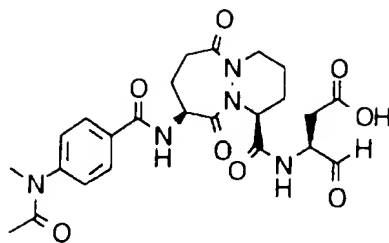


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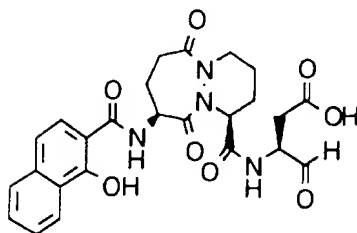


- 823 -

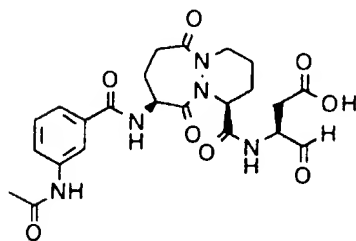
448



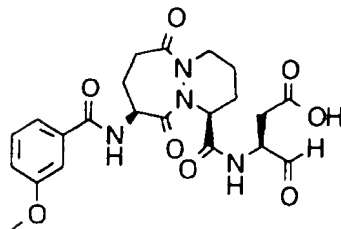
449



450

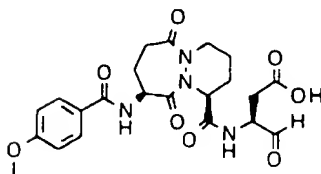


451



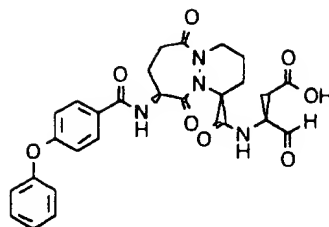
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452

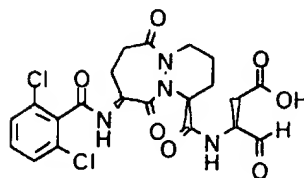


- 822 -

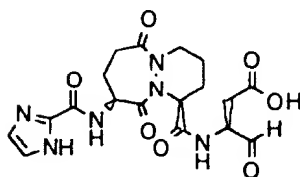
443



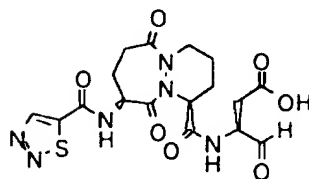
444



445

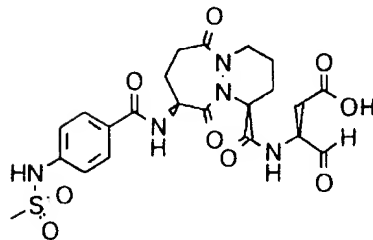


446



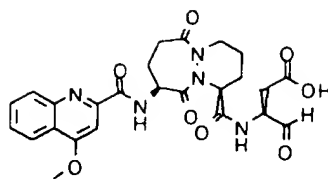
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447



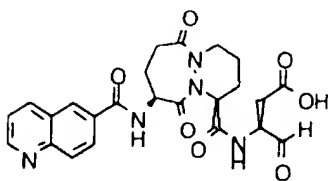
- 821 -

437



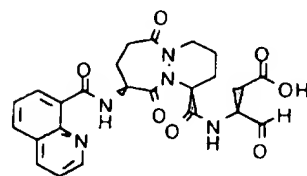
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438



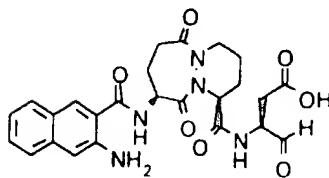
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439



;

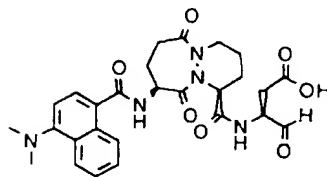
440



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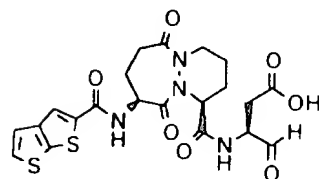
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441



;

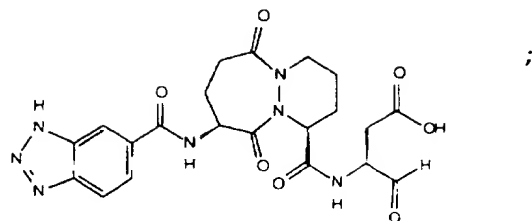
442



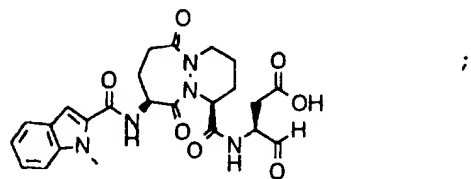
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- 820 -

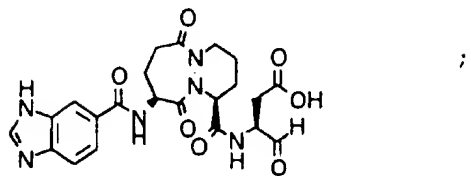
432



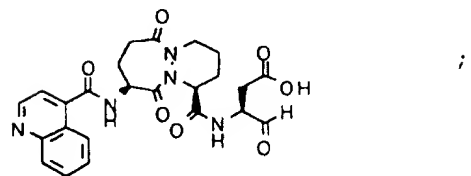
433



434

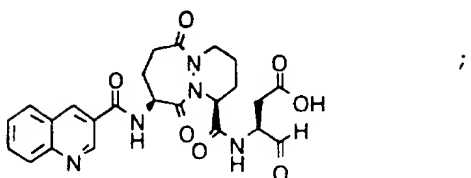


435



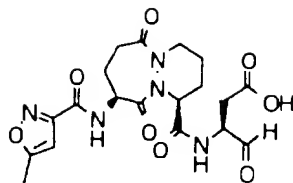
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436



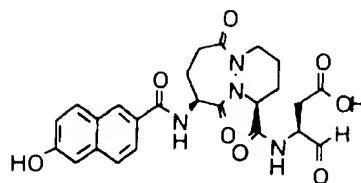
- 819 -

424



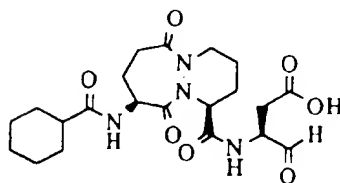
;

425



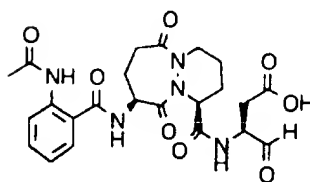
;

426



;

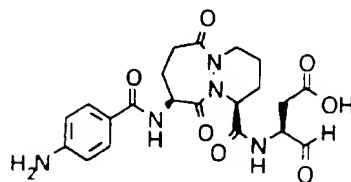
430



;

5

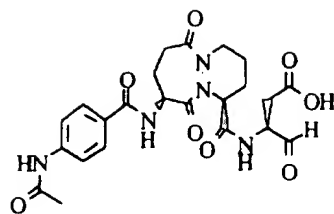
431



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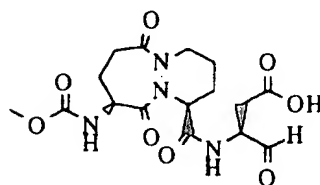
- 818 -

418



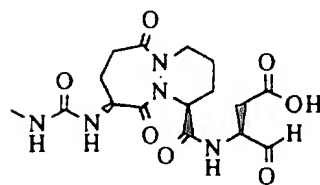
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419



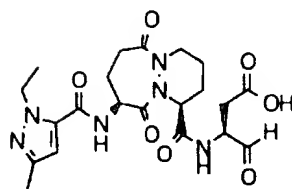
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420



;

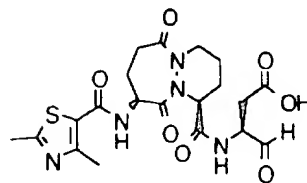
422



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5

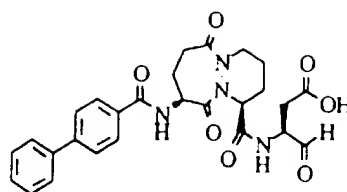
423



;

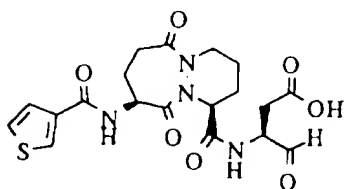
- 817 -

409



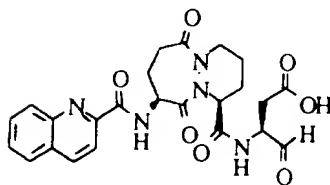
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410



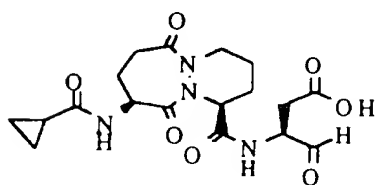
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411



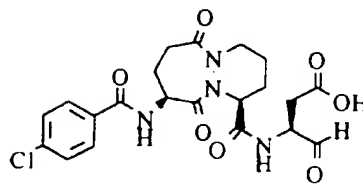
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413



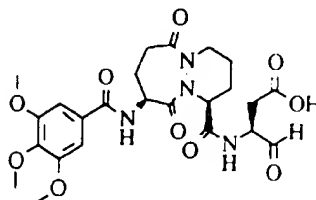
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416



1

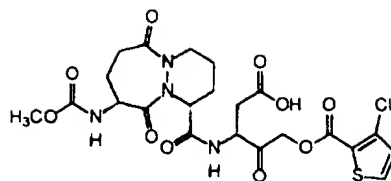
417



1

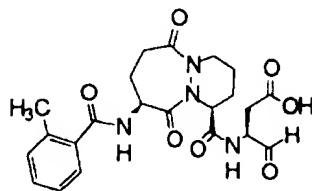
- 816 -

287



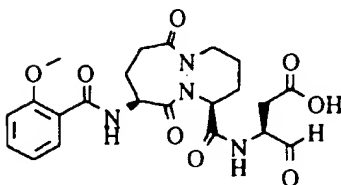
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404



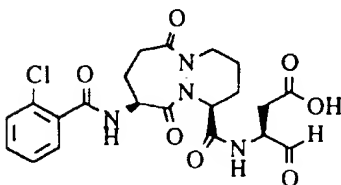
;

405



;

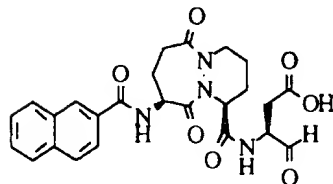
406



;

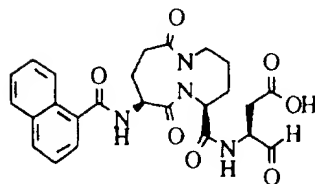
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407



;

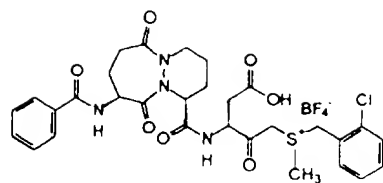
408



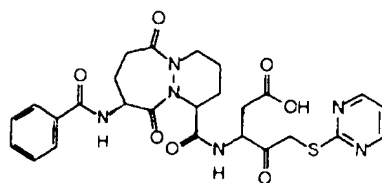
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- 815 -

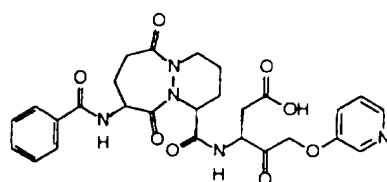
281



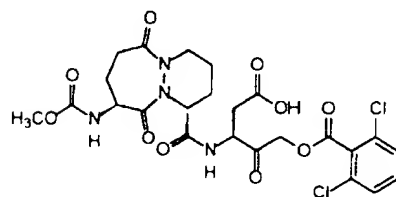
282



283

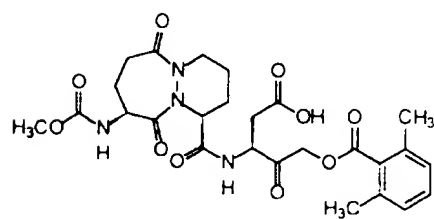


284

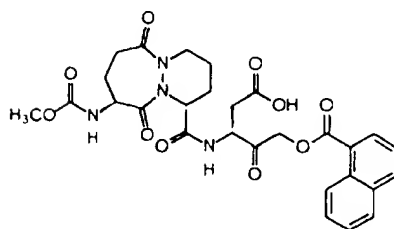


5

285

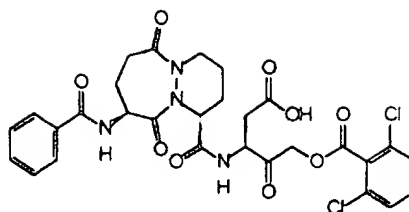


286

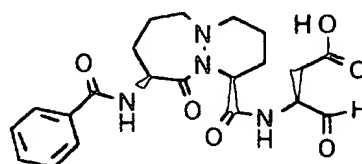


- 814 -

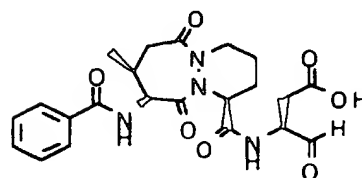
217e



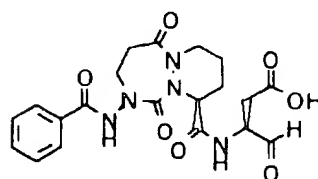
246



257

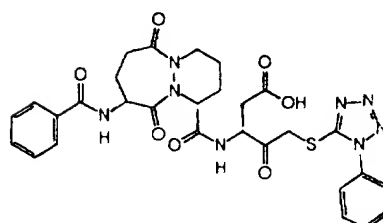


265



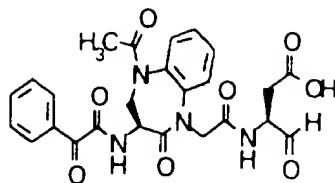
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280



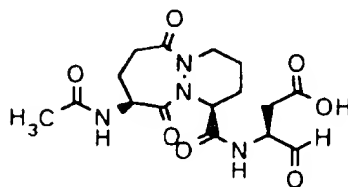
- 813 -

635



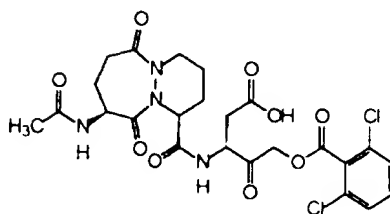
40. The compound according to claims 8 or 68, selected from the group consisting of:

214c



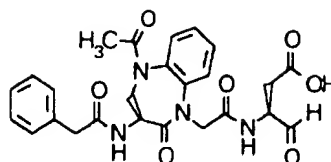
5

217c



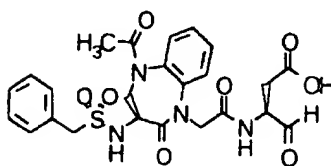
- 812 -

630



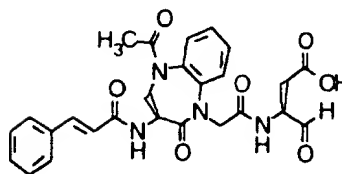
;

631



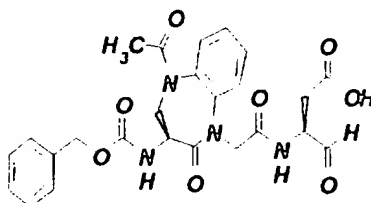
;

632



;

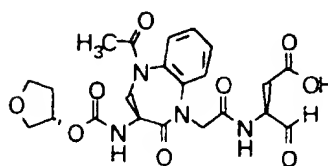
633



;

5

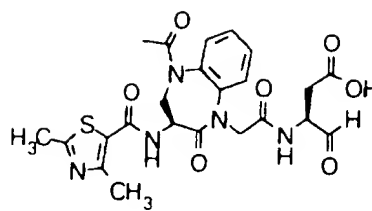
634



; and

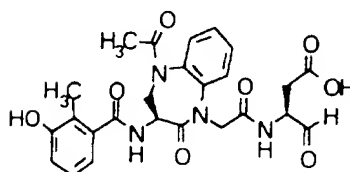
- 811 -

625



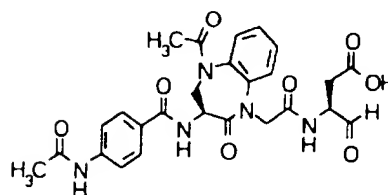
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626



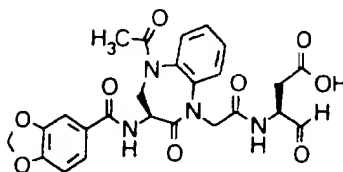
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627



;

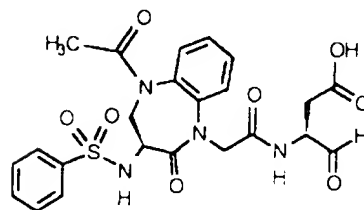
628



;

5

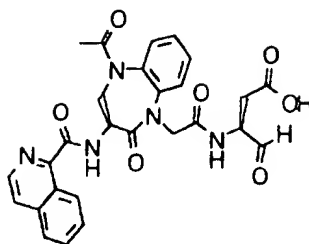
629



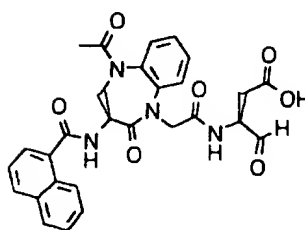
;

- 810 -

620

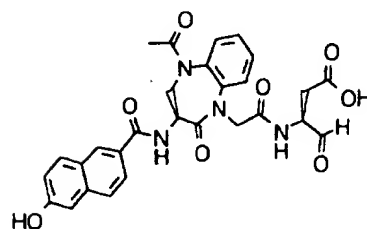


621



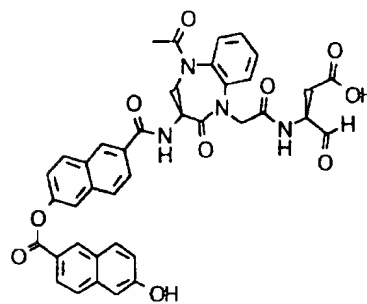
4

622



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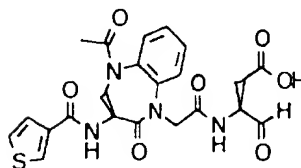
623



2

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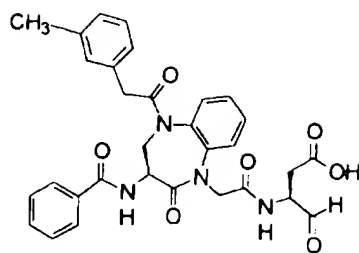
624



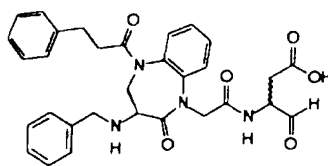
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- 809 -

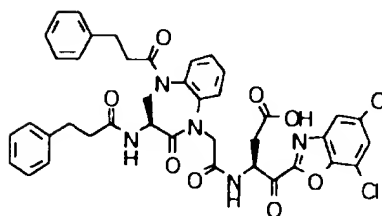
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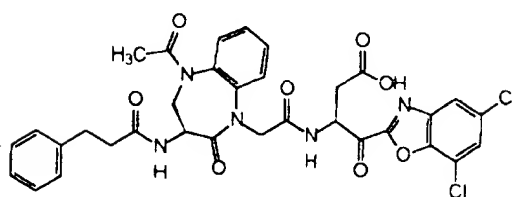


609a

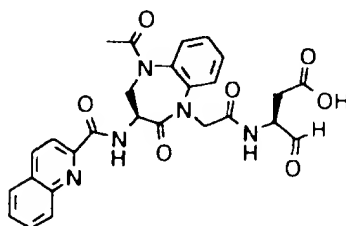


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609b

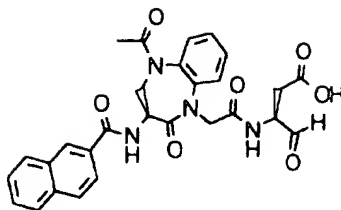


619



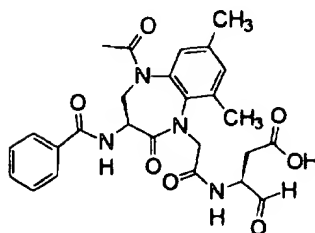
- 808 -

605n



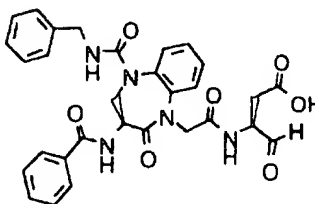
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605o



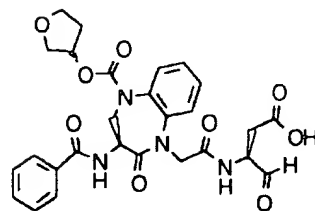
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605p



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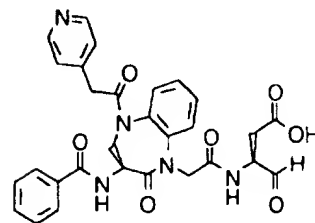
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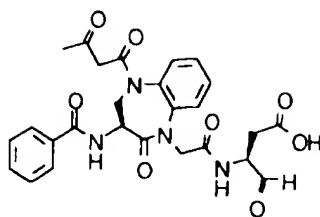
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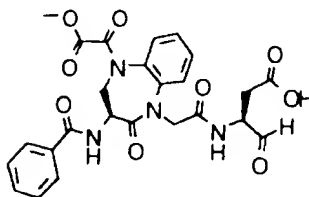
- 807 -

605g



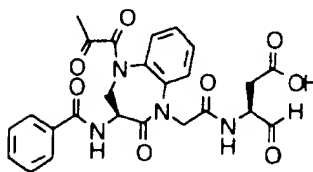
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605h



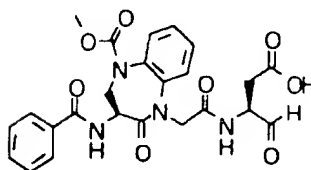
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605i



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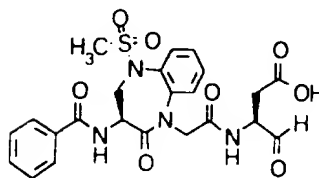
605j



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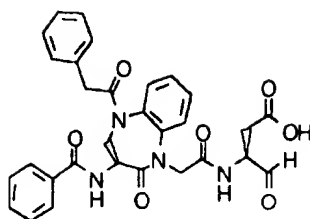
605m



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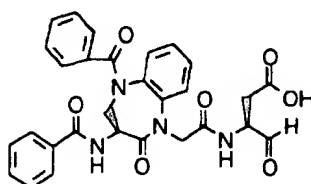
- 806 -

605b



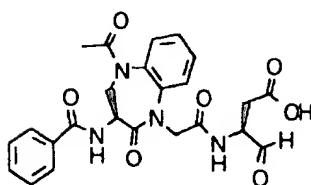
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605c



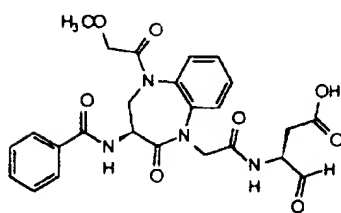
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605d



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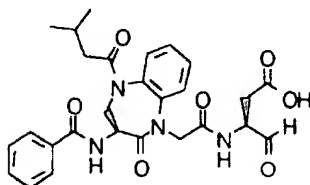
605e



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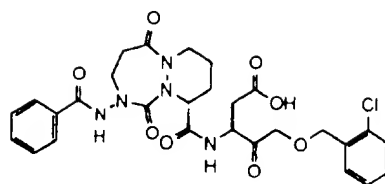
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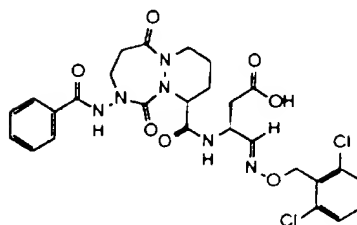
- 805 -

827e



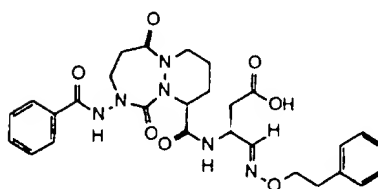
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907a



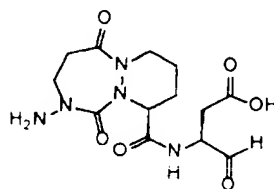
;

907b



; and

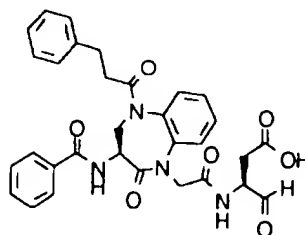
1029



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39. The compound according to claim 15
selected from the group consisting of:

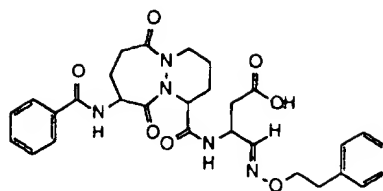
605a



;

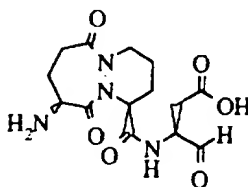
- 804 -

307b



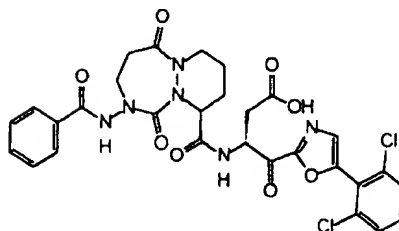
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429



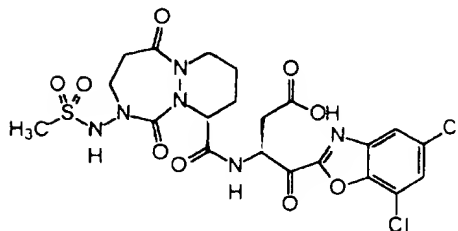
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820b



;

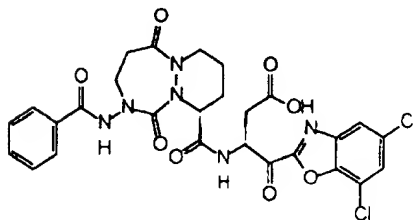
823b



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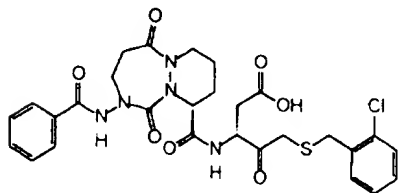
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823e



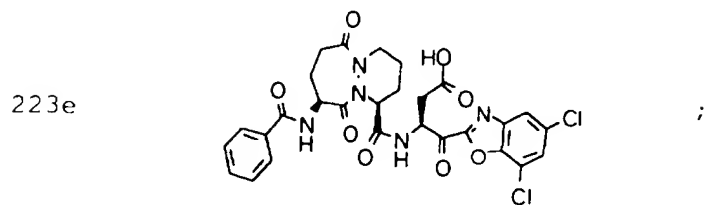
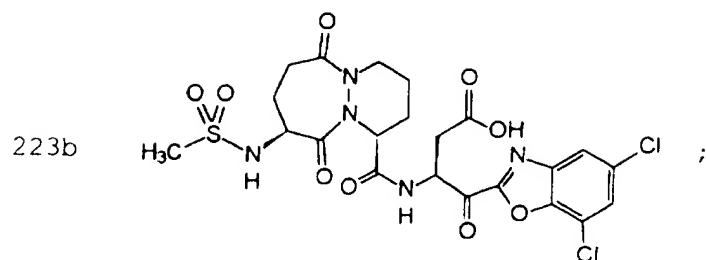
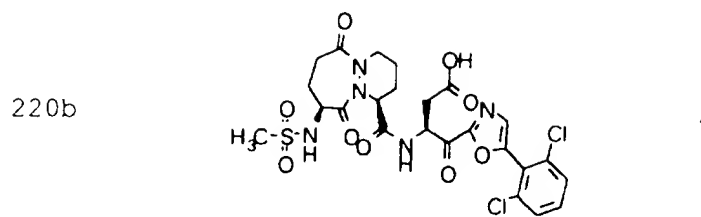
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826e

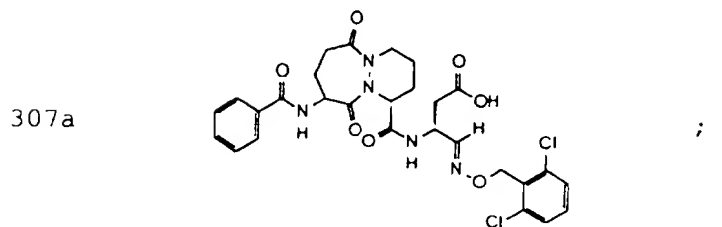
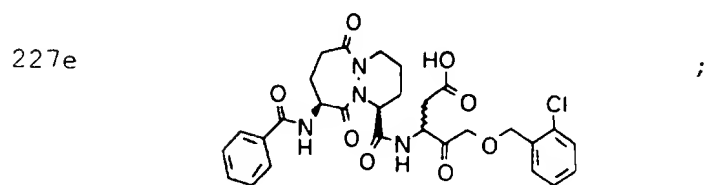
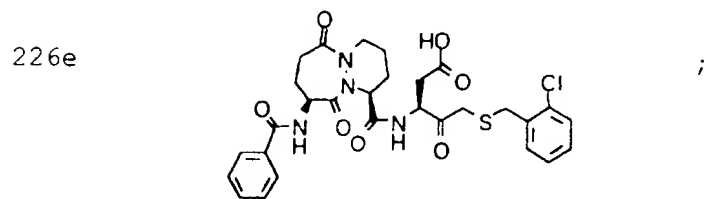


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- 803 -

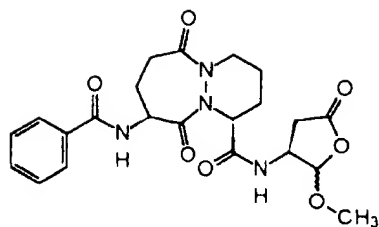


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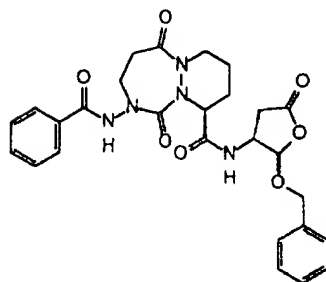
- 802 -

304a



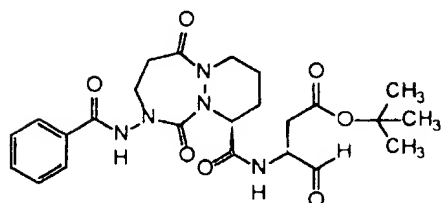
;

813e



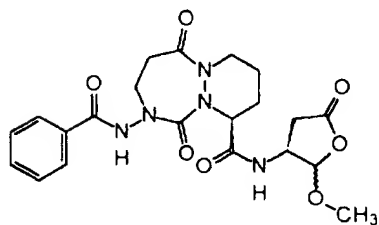
;

902



; and

904a



.

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38. The compound according to claims 8 or 68, selected from the group consisting of:

- 801 -

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

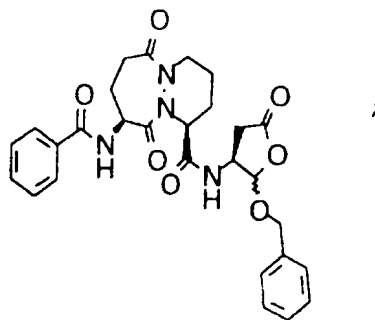


10 wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

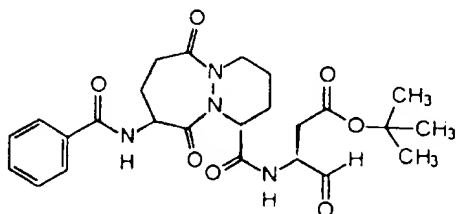
15 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

37. The compound according to claim 7 selected from the group consisting of:

20 213e



302



- 800 -

each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

- 5 each R₁₀ is independently selected from the group consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

- 10 R₁₃ is H or a C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, -CO₂H, wherein the R₉ is a C₁₋₄ branched or straight chain alkyl group; wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

- 15 R₂₁ is -H or -CH₃;

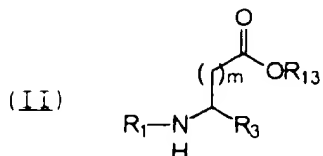
- each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, 20 thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

- each Ar₄ cyclic group is independently selected 25 from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

- 799 -

groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

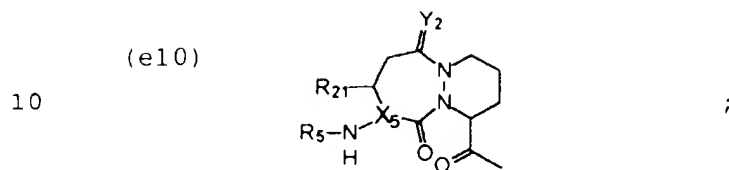
36. A compound represented by the formula:



5 wherein:

m is 1;

R_1 is:



R₃ is -CO-CH₂-T₁-R₁₁ and R₁₁ is -Ar₄;

R_5 is selected from the group consisting of:

$$-S(O)_2-R_9,$$
$$-S(O)_2-NH-R_{10},$$

15 $-C(C)-C(O)-R_{10},$

 $-R_9$, and
$$-C(O)-C(O)-OR_{10};$$
$$X_5 \leq 5 \text{ CH};$$
$$Y_2 \text{ is } 0;$$

20 T_1 is 0 or 5;

- 798 -

wherein the phenyl is optionally substituted with Q_1 ;

R_{21} is -H or -CH₃;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinoliny, isoquinoliny, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with -Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q_1 group which comprises one or more additional -Ar₃